CONTINUATION-IN-PART APPLICATION FOR
UNITED STATES PATENT

IN THE
UNITED STATES PATENT AND TRADEMARK OFFICE

(Attorney Docket No. IDR0108CIP-USA)

Title:

NOVEL SUBSTITUTED 2,3-BENZODIAZEPINE DERIVATIVES

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NOVEL SUBSTITUTED 2,3-BENZODIAZEPINE DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of Application Ser. No. 10/358,053, filed February 4, 2003.

BACKGROUND OF THE INVENTION

Field of Invention

[0001] The invention relates to new 2,3-benzodiazepine derivatives substituted by heterocycles, the acid addition salts thereof, as well as the pharmaceutical compositions containing them. The invention also relates to the use of said compounds as AMPA receptor antagonists.

Summary of Related Art

[0002] Over-activation of glutamate receptors has been associated with several acute and chronic diseases of the central nervous system ("CNS"). Various glutamate receptor antagonists have been investigated as therapeutic modalities (see for example Parsons *et al., Drug News Perspect.* 11:523 (1998) and Brăuner-Osborne *et al., J. Med. Chem.* 43:2609 (2000)).

[0003] AMPA (2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)-propionic acid) type glutamate receptors play a major role in a variety of central nervous system disorders. Inhibition of the activation of AMPA type receptors has been shown to have neuroprotective, antiepileptic and muscle-relaxant effects (see *e.g., Cerebrovasc. Brain Metab. Rev.* 6:225 (1994); *Neurology* 44 Suppl.8, S14 (1994); *J. Pharmacol. Exp. Ther.* 260:742 (1992)).

[0004] Glutamate receptors have been found not only in the CNS but also in peripheral tissues indicating therapeutic potential opportunities beyond the CNS (see *e.g.*, Skery *et al., Trends in Pharm. Sci.*, 22:74 (2001). Respiratory tract inflammation has been postulated to be beneficially influenced by NMDA-type glutamate antagonists (Said, *Trends in Pharm. Sci.* 20:132 (1999); and Said *et al., Trends in Pharm. Sci.*, 22:344 (2001)).

[0005] AMPA type receptors can be inhibited by various competitive and non-competitive antagonists. The therapeutic potential of non-competitive antagonists may be superior to that of competitive ones insofar as their activity is not dependent on high

concentrations of endogenous glutamate (see *e.g.*, Vizi *et al.*, *CNS Drug Rev*, 2:91 (1996)). One of the most prominent non-competitive AMPA receptor antagonists is 5-(4-aminophenyl)-8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (also designated as GYKI 52466) possessing remarkable antiepileptic, muscle relaxant and neuroprotective activities. (Tarnawa *et al.*, *Eur. J. Pharmacol.*, 167:193 (1989); Smith, *et al.*, *Eur. J. Pharmacol.*, 187:131 (1990); Quardouz *et al.*, *Neurosci. Lett.*, 125:5 (1991); Donevan *et al.*, *I. Neuron.*, 10:51 (1993)).

[0006] Several non-competitive AMPA antagonists have been described in the literature including 3,4-dihydro-5H- or 4,5-dihydro-3H-2,3-benzodiazepines, containing an acyl group at position 3 of the ring (see *e.g.*, Hungarian Patent Nos. 206,719 B and 219,777 B, U.S. Patent No. 5,536,832, European Patent Publication No. 0699 677 A1, and British Patent No. 2 311 779, as well as WO 96/04 283, WO 97/28 135, WO 99/07 707, WO 99/07 708 and WO 01/04 122). WO 96/06 606 (corresponding to U.S. Patent No. 5,795,886) describes several 2,3-benzodiazepine derivatives having aryl and heteroaryl substituents (*e.g.*, pyridyl, thienyl, furyl, phenyl, imidazolyl, benzimidazolyl, *etc.*) at C3.

[0007] The compounds listed above have been found to be particularly useful in diseases in which the over-function of the glutamate system can be detected. Such acute disorders of the CNS include for example stroke, brain ischemia, brain and spinal cord injuries, perinatal hypoxia, hypoglycemic nervous damage, *etc.* Additional chronic illnesses in which selected AMPA antagonists can be applied include *e.g.*, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS-induced dementia, glaucoma, diabetic retinopathy as well as Parkinson's disease. Furthermore, enhanced activity of the glutamate system has also been shown in conditions associated with neural damage (*e.g.*, epilepsy, migraine, urinary bladder incontinence, psychosis -- anxiety, schizophrenia *etc.*, drug-abuse, pathological pain, brain edema and tardive dyskinesia) implying an impressive therapeutic potential for AMPA antagonists.

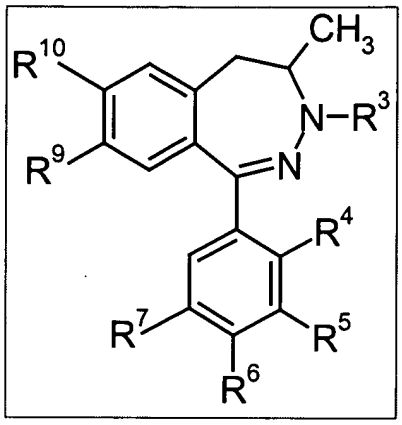
[0008] Recently, experimental data suggested that selected AMPA antagonists have beneficial effect on the autoimmune encephalomyelitis elicited in rats, which is the accepted model of multiple sclerosis (Smith *et al.*, *Nature Medicine* 6:62 (2000)). In addition, AMPA and NMDA receptors in the spinal cord have been implicated in the contraction of the bladder and the urethra, suggesting that AMPA antagonists may be useful in the treatment of urinary incontinence (Nishizawa *et al.*, *Adv in Exp. Med. & Biol.* 4:275 (1999)).

[0009] Two 2,3-benzodiazepine derivatives GYKI 52466 (*supra*), and (R)-7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (GYKI 53773, also known as Talampanel) were beneficial. The latter has proved to be active in clinical trials on epilepsy patients (Bialer *et al.*, *Epilepsy Res.* 43:11 (2001)).

[0010] In addition, GYKI 52466 has been reported to inhibit growth of selected tumor cell types (colon adenocarcinoma, astrocytoma, breast carcinoma, lung carcinoma and neuroblastoma) (Rzeski *et al.*, *Proc. Nat. Acad. Sci.* 98:6372 (2001)).

SUMMARY OF THE INVENTION

[0011] The invention relates to new 2,3-benzodiazepine derivatives of formula (I) below, isomers and acid addition salts thereof and to pharmaceutical compositions containing the same,



(I)

wherein the substituent meanings are as follows:

R^3 represents a substituted or unsubstituted 5- or 6-membered, aromatic, saturated or partially saturated heterocyclic ring containing at least 2 heteroatoms, in which the heteroatom can be oxygen-, sulfur- or nitrogen atom and in the case when the heterocyclic ring contains 2 heteroatoms one of them is different from nitrogen;

R^4, R^5, R^6 and R^7 independently from each other represent hydrogen atom, halogen atom, C_1-C_3 alkyl group, nitro group or amino group, wherein the amino group can be substituted independently from each other with one or two C_1-C_3 alkyl group, C_2-C_5 acyl group, or C_2-C_5 alkoxycarbonyl group, or aminocarbonyl group, or C_2-C_5 alkylaminocarbonyl group; and

R^9 represents C_1-C_3 alkoxy group or halogen atom

R^{10} represents hydrogen or halogen atom or

R^9 and R^{10} together can be C_1-C_3 alkylendioxy group.

[0012] Representative compounds include, without limitation, (R)-5-(4-aminophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-8-methyl-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-

h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-7-(4,5-dihydro-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-7-(5-ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-8-methyl-7-(5-methyl-1,3,4-oxadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-methylphenyl)-7-(5-ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-(5-propyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzo-diazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-(5-methoxymethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-{5-[1-(1E)-propen-1-yl]-1,3,4-thiadiazol-2-yl}-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-chlorophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine; and (R)-5-(4-amino-3-chlorophenyl)-8-methyl-7-(5-methoxymethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine and the acid addition salts thereof.

[0013] The invention also discloses pharmaceutical compositions comprising a compound of formula (I) as the active ingredient, wherein the meaning of R^3-R^7, R^9 and R^{10} is as defined herein, or a steroisomer or a pharmaceutically acceptable salt thereof together with pharmaceutically acceptable solvents, diluents, carriers and filling materials.

[0014] The compounds are suitable for treating conditions associated with muscle spasms, epilepsy, acute and chronic forms of neurodegenerative diseases as well as preventing, treating or alleviating the symptoms of acute and chronic inflammatory disorders.

[0015] One of skill will appreciate, in light of the many publications relating to the expanding therapeutic values of AMPA type receptor antagonists, that the compounds of the invention are useful in a very large number of unrelated conditions.

[0016] Hence, methods for treating glutamate dysfunction associated with an acute or chronic neurodegenerative disease or in acute or chronic disease of the eyes associated with glutamate dysfunction are provided. Representative neurodegenerative disorders include, for

example, cerebral ischemia (stroke), brain and spinal cord trauma, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS-induced dementia, essential tremor, Parkinson's disease, multiple sclerosis and urinary incontinence. Acute or chronic disorders of the eyes associated with glutamate dysfunction include glaucoma or diabetic retinopathy. Disclosed also are methods for treating epilepsy, reducing muscle spasms, reducing pain, or inflammatory disorders which comprise administering to the subject in need of such treatment a therapeutically effective amount of the compounds of the invention. Included among the inflammatory disorders are allergic inflammatory disorders of the airways which can encompass allergic rhinitis, intrinsic or extrinsic asthma bronchiale, acute or chronic bronchitis, chronic obstructive pulmonary disease and pulmonary fibrosis.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The patents, published applications, and scientific literature referred to herein establish the knowledge of those skilled in the art and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually indicated to be incorporated by reference. Any conflict between any reference cited herein and the specific teachings of this specifications shall be resolved in favor of the latter. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this specification shall be resolved in favor of the latter.

[0018] The invention discloses novel substituted 2,3-benzodiazepine derivative compounds and methods of making the same. Pharmaceutical compositions employing the novel substituted 2,3-benzodiazepine derivative compounds and their use for the treatment for a number of disease conditions are also disclosed.

[0019] Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th Ed., McGraw Hill Companies Inc., New York (2001). Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention. However, preferred materials and methods are described. Materials, reagents and the like to which reference are made in the

following description and examples are obtainable from commercial sources, unless otherwise noted.

[0020] As used in this specification, the singular forms "a", "an" and "the" specifically also encompass the plural forms of the terms to which they refer, unless the content clearly dictates otherwise. For example, reference to "an antagonist" includes mixtures of antagonists.

[0021] As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

[0022] The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

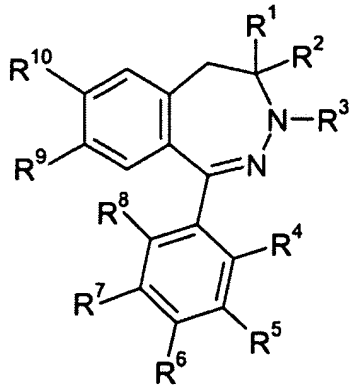
[0023] As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or".

[0024] As used herein, the recitation of a numerical range for a variable is intended to convey that the invention may be practiced with the variable equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable can be equal to any integer value of the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable can be equal to any real value of the numerical range, including the end-points of the range. As an example, a variable which is described as having values between 0 and 2, can be 0, 1 or 2 for variables which are inherently discrete, and can be 0.0, 0.1, 0.01, 0.001, or any other real value for variables which are inherently continuous.

[0025] The methods of the present invention are intended for use with any mammal that may experience the benefits of the methods of the invention. Foremost among such mammals are humans, although the invention is not intended to be so limited, and is applicable to veterinary uses. Thus, in accordance with the invention, "mammals" or "mammal in need" include humans as well as non-human mammals, particularly domesticated animals including, without limitation, cats, dogs, and horses.

[0026] It will be understood that the subject to which a compound of the invention is administered need not suffer from a specific traumatic state. Indeed, the compounds of the invention may be administered prophylactically, prior to any development of symptoms. The term "therapeutic", "therapeutically", and permutations of these terms are used to encompass therapeutic, palliative as well as prophylactic uses. Hence, as used herein, by "treating or alleviating the symptoms" is meant reducing, preventing, and/or reversing the symptoms of the individual to which a compound of the invention has been administered, as compared to the symptoms of an individual receiving no such administration.

[0027] Benzodiazepines of formula (II) below, and the isomers as well as the acid addition salts thereof, are the subject of Patent Application No. 10/358,053:



(II)

wherein

R^1 and R^2 independently of each other represent hydrogen atom or C_1-C_3 alkyl group,

R^3 represents substituted or unsubstituted 5- or 6-membered, aromatic, saturated or partially saturated heterocyclic ring containing at least 2 hetero atoms, in which the hetero atom can be oxygen-, sulfur- or nitrogen atom and in the case when R^3 is a 5-membered ring one of the heteroatoms is different from nitrogen;

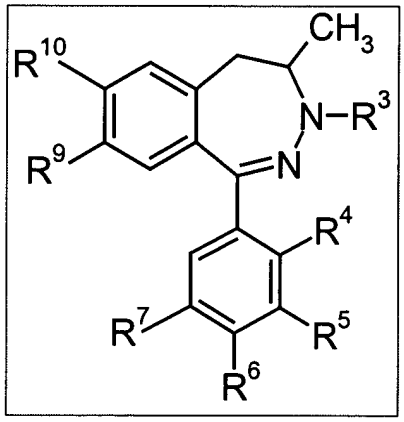
R^4, R^5, R^6, R^7 and R^8 independently from each other represent hydrogen atom, halogen atom, C_1-C_3 alkyl group, nitro group or amino group, wherein the amino group can be substituted independently from each other with one or two C_1-C_3 alkyl group, C_2-C_5 acyl group, or C_2-C_5 alkoxycarbonyl group, or aminocarbonyl group, or C_2-C_5 alkylaminocarbonyl group,

R^9 represents C_1-C_3 alkoxy group or halogen atom,

R^{10} represents hydrogen or halogen atom or

R^9 and R^{10} together can be C_1-C_3 alkylendioxy group.

[0028] The present invention is directed to 2,3-benzodiazepine derivatives of formula (II) as shown below in formula (I):



(I)

wherein R^1 and R^8 are hydrogen, R^2 is CH_3, the meaning of R^4, R^5, R^6, R^7, R^9 and R^{10} is as defined above, R^3 is a moiety selected from the group consisting of substituted or unsubstituted isoxazole, isothiazole, thiazole, thiazoline, 4-thiazolinone, oxazole, oxazoline, 1,2,3-thiadiazole, 1,3,4-thiadiazole, 1,3,4-thiadiazolin-2-one, 1,2,4-thiadiazolin-3-one, 1,4,2-oxathiazoline, 1,3,4-oxadiazole, 1,2,3-triazole, 1,3,4-triazole, 1,2,3,4-thiatriazole,.tetrazole, 1,3-thiazin-4-one and 1,3,4-thiadiazin-4-one ring.

[0029] The heterocyclic substituent of the benzodiazepine ring as R^3 can be further substituted – among others – with one or more C_1-C_6 alkyl group, C_2-C_3 alkenyl, a C_3-C_7 cycloalkyl, a trifluoromethyl, a C_1-C_3 alkoxy or a phenyl group, an oxo, a formyl, a carboxyl

or a C_2-C_4 alkoxycarbonyl group, a C_1-C_3 alkoxymethyl group, a hydroxymethyl group, whrerein the hydroxy group can be alkylated or acylate, a C_1-C_3 alkylthiomethyl group, a cyanomethyl group or an aminomehtyl group, wherein the amino group can be alkylated or acylated.

[0030] The meaning of alkyl group encompasses both straight and branched chain alkyl groups. The meaning of alkenyl group can be vinyl, 1-propenyl or 2-propenyl group. The meaning of halogen atom can be fluorine, chlorine, bromine, or iodine atom. The amino group can be unsubstituted or substituted with one or two alkyl groups, as well as acylated with aliphatic or aromatic carboxylic acid or any kind of carbonic acid esters.

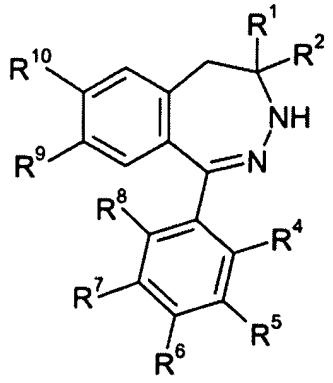
[0031] In the case of compounds of formula (I), the term "isomers" means both enantiomers, as well as the E and Z isomers if applicable, furthermore, isomers shall include diastereomers, tautomers and mixture of them, for example racemic mixture.

[0032] Salts of the compounds of formula (I) relate to physiologically acceptable salts formed with inorganic or organic acids. Suitable inorganic acids can be, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid. Suitable organic acids can be, for example, formic acid, acetic acid, maleic and fumaric acid, succinic acid, lactic acid, tartaric acid, citric acid or methanesulfonic acid.

[0033] Representative compounds of formula (I) include, without limitation, (R)-5-(4-aminophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-8-methyl-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-7-(4,5-dihydro-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-7-(5-ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-aminophenyl)-8-methyl-7-(5-methyl-1,3,4-oxadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzo-diazepine; (R)-5-(4-amino-3-methylphenyl)-7-(5-ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-(5-propyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzo-diazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-

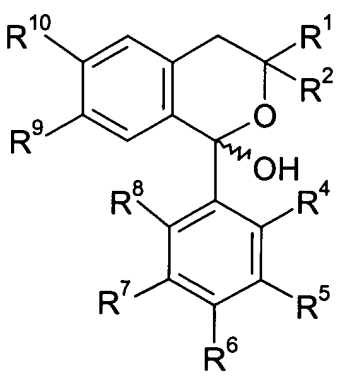
h][2,3]benzodiazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-(5-methoxymethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-methylphenyl)-8-methyl-7-{5-[1-(1E)-propen-1-yl]-1,3,4-thiadiazol-2-yl}-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine; (R)-5-(4-amino-3-chlorophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine; and (R)-5-(4-amino-3-chlorophenyl)-8-methyl-7-(5-methoxymethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine and the acid addition salts thereof.

[0034] The compounds of formulas (I) and (II) can be prepared in the following way. The heterocycle corresponding to R^3 is built up starting from a compound of formula (III) below:

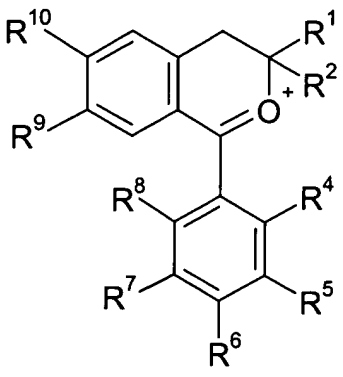


(III)

wherein R^1-R^{10} are defined for formulas (I) and (II) above, by known methods or a compound having the following formula (IV) or the following isochromenilium salt having formula (IVa) which is formed from the compound of formula (IV) , wherein the meaning of R^1, R^2 , R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} is as defined above :

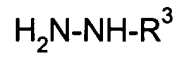


(IV)

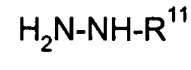


(IVa)

A compound of formulas (IV) or (IVa) is reacted with a compound having formula (V) or (VI):

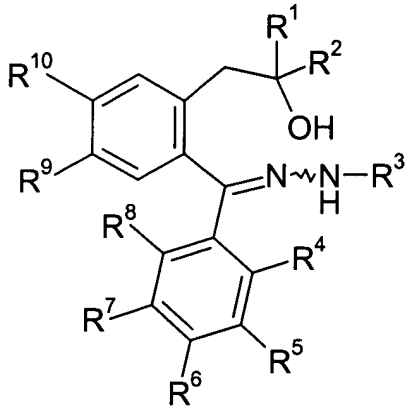


(V)

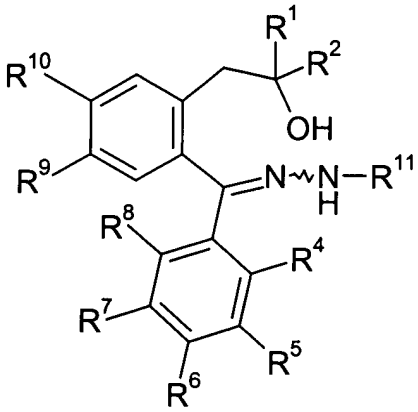


(VI)

wherein the meaning of R^3 is as defined above and the meaning of R^{11} is C_2-C_8 alkoxycarbonyl or aryl alkoxycarbonyl group to obtain the compounds of formulas (VII) or (VIII).

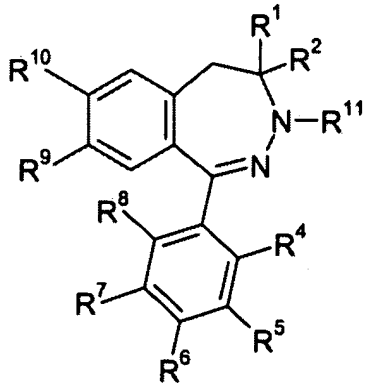


(VII)



(VIII)

[0035] The hydroxyl group of the compounds of formulas (VII) or (VIII) is transformed into a sulfonate ester, and the latter intermediate is submitted to ring-closure resulting in compounds of formulas (I), (II) or (IX):



(IX)

by applying a strong base. Alternatively, the compounds of formulas (VII) or (VIII) are transformed into compounds of formulas (I), (II) or (IX) according to Mitsunobu (*Synthesis*, I:1 (1988)). In the compound of formula (IX), the R^{11} group is cleaved to give the compound of formula (III), which is converted into the compound of formulas (I) or (II) according to the method described in process as described above. Then, if desired, in a compound of formula (I) or (II) obtained according to any of the above processes, the nitro group is reduced or the amino group is acylated, alkylated, or after diazotation, is exchanged by a halogen atom or hydrogen atom, or a halogen atom is exchanged by an amino group and in this way it is transformed into another compound of formula (I) or (II) and/or the isomers are separated and, if desired, salts are formed.

[0036] The compounds of formulas (III) and (IX) are chiral compounds, and therefore formulas (III) and (IX) refers to either of the individual enantiomers or mixtures thereof. The hemiketal type compounds of formula (IV) as well as the hydrazone derivatives of formulas (VII) and (VIII) represent different stereoisomers and they refer to all of the individual stereoisomers and mixtures thereof. The R^{11} group can be a C_2-C_8 alkoxycarbonyl group, such as a tert-butoxycarbonyl or a benzyloxycarbonyl group.

[0037] The starting materials of formula (III) are known in the literature (U.S. Patent No. 5,536,832 and British Patent No. 2,311,779, as well as WO 97/28 135 and WO 01/04 122). Hungarian Patent No. 219,777 and British Patent No. 2,311,779 describe the synthesis of optically active compounds of formula (III) as well.

[0038] The optically active compounds of formula (III) can be synthesized by reacting a hemiketal of formula (IV) – prepared for example from an optically active substituted phenyl-isopropanol according to Anderson *et al.* (*J. Am Chem Soc.* 117:12358 (1995)) – with an alkoxycarbonyl-hydrazide containing an easily removable alkoxycarbonyl group, such as a tert-butoxy-carbamate in the presence of catalytic amount of an acid. The hydrazone of formula (VIII) obtained after isolation then is transformed into a mesyl ester *e.g.*, with methanesulfonyl chloride in the presence of triethylamine, and the latter is treated with base, for example sodium hydroxide, in alcoholic solution to yield the benzodiazepine derivative of formula (IX) in a ring closure reaction. Then the substituent of the N-3 atom (numbering according to the benzodiazepine ring) is cleaved, *e.g.*, by hydrolysis or another method, for example hydrogenolysis, to yield the desired compound of formula (III). The cleavage of the tert-

butoxycarbonyl group may be carried out with trifluoroacetic acid, hydrogen bromide or zinc bromide in dichloromethane.

[0039] The heterocyclic moiety – corresponding to the R^3 substituent – of the compound of formula (I) or (II) is synthesized starting from the compounds of formula (III) according to methods known in the art relating to heterocyclic chemistry.

[0040] Some of the compounds of formula (I) or (II) can be synthesized, for example, from the 4,5-dihydro-2,3-benzodiazepine derivatives substituted with thiocarbamoyl group at position 3 of the benzodiazepine ring. Latter compounds can be obtained from 4,5-dihydro-3H-2,3-benzodiazepine derivatives of formula (III), for example with potassium thiocyanate in acetic acid medium. The thus-obtained 4,5-dihydro-3-thiocarbamoyl-3H-2,3-benzodiazepines are reacted with α-halo ketones or α-halo aldehyde acetals to yield 2,3-benzodiazepine derivatives having a substituted or unsubstituted 2-thiazolyl group. In an analogous reaction, if 2-halo carboxylic acid esters are used instead of the α-halo oxo-compound, the appropriate compounds containing a 3-thiazolinone ring are formed.

[0041] When the above-mentioned 4,5-dihydro-2,3-benzodiazepines containing thiocarbamoyl group in position 3 are reacted with β-halo carboxylic acid esters, for example ethyl 3-bromopropionate, then new 2,3-benzodiazepine derivatives substituted with 5,6-dihydro-[1,3]thiazin-4-one ring are obtained.

[0042] The compounds of formula (I) or (II) containing 1,3,4-thiadiazole group as R^3 substituent can be synthesized for example by the following way. First, a trimethylsilyl derivative is prepared from a 4,5-dihydro-3H-[2,3]benzodiazepine of formula (III), which is then reacted with thiophosgene to give thiocarboxylic acid chloride. Finally, the latter is treated with hydrazine to yield the thiocarboxylic acid hydrazide derivatives. The 2,3-benzodiazepine derivatives substituted with carbothiohydrazide group are reacted with an acid anhydride or chloride and the thus-obtained partially occurring ring closure of the carbothio-N-acylhydrazides is promoted by further acid treatment to yield [1,3,4]thiadiazolyl-2,3-benzodiazepines. Another procedure for the synthesis of the latter compounds is to react the above-mentioned intermediate thiocarboxylic acid chloride with an acid hydrazide, and then the resulting carbothiohydrazide derivative containing an acyl group on the terminal N-atom is treated with acid to give the cyclic product.

[0043] In an analogous reaction benzodiazepines of formula (I) or (II) containing a [1,3,4]oxadiazole ring can be obtained, for example, if the above mentioned N-acyl-thiocarboxylic acid hydrazide derivative is treated with a sulfur binding reagent, for example mercury (II) acetate.

[0044] The 4,5-dihydro-2,3-benzodiazepin-3-carbothiohydrazides can serve as starting materials for further new compounds of formula (I) or (II) substituted with a hetero-ring. For example, if the N-methyl-carbamoyl-carbothiohydrazide obtained with methyl isocyanate is heated with concentrated acid, for example hydrochloric acid, then new compounds of formula (I) or (II) substituted with (5-oxo-4,5-dihydro-[1,3,4]thiadiazol-2-yl) group can be obtained. If the carbothiohydrazide derivative is reacted with bromoacetic acid ester, (5-oxo-5,6-dihydro-4H-[1,3,4]thiadiazin-2-yl)-[2,3]benzodiazepine derivatives having a 6-membered ring as the R_3 substituent are obtained. If the carbothiohydrazide derivatives are reacted with a α-halo-ketones, for example chloroacetone, then *e.g.*, (5-methyl-6H-[1,3,4]thiadiazin-2-yl)-[2,3]benzodiazepines are formed.

[0045] The appropriate thiohydroxamic acids can be obtained from [2,3]benzodiazepin-3-thiocarboxylic acid chlorides with hydroxylamine, which can be transformed into heterocyclic compounds by reacting with bifunctional alkylating agents. Among others, [1,4,2]oxathiazol-3-yl-2,3-benzodiazepines can be synthesized for example from thiohydroxamic acid derivatives with methylene iodide.

[0046] The compounds of formula (I) or (II) containing 3-oxo-2,3-dihydro-[1,2,4]thiadiazol-5-yl group as R^3 substituent can be prepared, for example, by reacting the unsubstituted compounds of formula (III) with phenoxycarbonyl isothiocyanate, then the resulting phenoxycarbonyl-thiocarbamoyl-benzodiazepine transformed into N-alkyl-carbamoyl-thiocarbamoyl-benzodiazepine with primary amines and the latter is reacted *e.g.*, with bromine to accomplish the ring closure between the sulfur and the nitrogen atoms.

[0047] The compounds of formula (I) or (II) containing 4,5-dihydro-oxazol-2-yl group as an R^3 substituent can be synthesized by reacting the compounds of formula (III) with chloroethyl isocyanate to give an urea derivative, which is heated in the presence of sodium iodide and potassium carbonate in dimethylformamide to accomplish the ring closure.

[0048] The compounds of formula (I) or (II) containing 2-alkyl-thiazol-4-yl group as R^3 substituent can be synthesized by reacting 3-bromo-acetyl-[2,3]benzodiazepines with the appropriate carboxylic acid thioamide.

[0049] From 3-cyano-2,3-benzodiazepines – obtained from 2,3-benzodiazepines of formula (III) with cyanogen bromide – 2,3-benzodiazepines containing among others (1H-tetrazol-5-yl) as well as (5-alkyl-[1,2,4]oxadiazol-3-yl) groups as an R^3 substituent can be synthesized. The tetrazolyl compounds can be synthesized by reacting the nitrile derivative with sodium azide in dimethylformamide in the presence of ammonium chloride, while if the nitrile compound is first treated with hydroxylamine and the thus-obtained amidoxime is reacted with a carboxylic acid anhydride or chloride, then the appropriate 1,2,4-oxadiazolyl compounds can be obtained.

[0050] The compounds of formula (I) or (II) containing 1,2,4-triazolyl group as R^3 substituent can be synthesized from a 3-thiocarbamoyl-[2,3]benzodiazepine derivative by reacting first with methyl iodide, then the obtained S-methyl compound is condensed with hydrazine and the so formed intermediate is treated with a carboxylic acid anhydride or chloride.

[0051] Other illustrative processes for the synthesis of compounds of formula (I) or (II) are those, where a hemiketal of formula (IV) is reacted with a heterocyclic reagent substituted with a hydrazine group in the presence of an acid as catalyst. The condensation reaction can be carried out in the presence of hydrochloric acid as catalyst by heating *e.g.,* in isopropanol or toluene and possibly with a Dean-Stark apparatus. It can be advantageous in some instances to first transform the hemiketal into an isochromenilium salt of formula (IVa) with a mineral acid *e.g.,* perchloric acid and the latter is reacted with a hydrazine reagent, for example in isopropanol. The thus- obtained hydrazones of formula (VII) are generally formed as a mixture of stereoisomers. They can be further reacted *e.g.,* with methanesulfonyl chloride in dichloromethane in the presence of triethylamine, and the mesylate obtained after isolation is treated with a concentrated solution of a base in an alcohol or a mixture of alcohol – dichloromethane. The ring closure reaction can be achieved for example, by the Mitsunobu reaction (Mitsunobu *Synthesis* 1:1 (1981)) as well.

[0052] If desired, the compounds of formula (I) or (II) obtained by different methods can be transformed into other compounds of formula (I) or (II) with further reactions. For example, a reactive halogen atom in the side chain of the heterocycle – the R^3 substituent -- can

be exchanged for an amino group, for example by heating with an excess of a proper amine, or the NH group of a N-containing heterocyclic compound can be alkylated by known methods. The latter transformation for example in the case of a triazolyl compound, can be carried out with methyl iodide in the presence of potassium tert-butoxide.

[0053] The reduction of the nitro group in the compounds of formula (I) or (II) is generally carried out in polar solvents at room temperature or at elevated temperature in the presence of catalysts such as Raney-nickel, platinum or palladium. Besides gaseous hydrogen, other hydrogen sources *e.g.*, hydrazine hydrate, ammonium formate, potassium formate or cyclohexene can also be applied. The nitro group can be reduced, for example, with tin in the presence of an acid, or with tin (II) chloride by heating in an alcohol as well. The amino group can be further derivatised by known methods, for example alkylation, acylation, or Sandmeyer reaction.

[0054] The AMPA antagonistic activity of the compounds of formula (I) or (II) of the present invention is exemplified by the following experiments. Reference to compounds by number refers to compounds described in the numbered examples below.

Inhibition of the AMPA receptors

[0055] Two experimental models were used for the demonstration of the inhibition of the AMPA receptor activation of the compounds of formula (I) or (II). In the first model the spreading depression caused by glutamate agonists (*i.e.*, AMPA or kainate) was studied, while in the second one the transmembrane ion-current induced by the activation of the AMPA/kainate receptors was measured directly.

Inhibition of AMPA induced "spreading depression" in isolated chicken retina-

[0056] The AMPA antagonistic effect of the compounds of formula (I) or (II) was studied in the *in vitro* "spreading depression" model (Sheardown *Brain Res.* 607:189 (1993)). The AMPA antagonists prolong the latency of the development of the "spreading depression" caused by AMPA (5 μM).

Table 1
Inhibition of the "spreading depression" in chicken retina

Compound (Number of example) / IC_{50} μM					
GYKI 52466 (reference)	**GYKI 53773** (reference)	**61**	**69**	**86**	**84**
9.5	1.2	1-5	0.9	0.42	0.85

[0057] The data of Table 1 indicate that the compounds of the present invention inhibit the AMPA-induced "spreading depression" with an IC_{50} value of 0.4-5 μM.

Inhibition of AMPA induced transmembrane currents

[0058] The activity of the compounds of the present invention was studied on acutely isolated cerebellar Purkinje cells by measuring the whole-cell current induced by 5 μM AMPA according for example to the method described by Bleakman *et al.* (*Neuropharmacology* 12:1689 (1996)). According to the IC_{50} values obtained, the compounds of the present invention inhibit the AMPA-induced ion-current by one to two magnitudes greater than the internationally accepted reference compound GYKI 52466 (5-(4-aminophenyl)-9H-1,3-dioxolo[4,5-h][2,3]-benzodiazepine, Hungarian patent No. 191 698), or GYKI 53773 ((R)-7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine, U.S. Patent No. 5,536,832), the IC_{50} values of which are 8.8 μM, and 1.57 μM, respectively. (See Table 2).

Table 2.

Inhibition of the ion-currents caused by 5 μM AMPA determined by the whole cell patch clamp method

Compound (Number of example) / IC_{50} μM					
GYKI 52466 (reference)	GYKI 53773 (reference)	61	69	86	84
8.8	1.57	0.49	0.42	0.06	0.09

Anticonvulsant activity

[0059] Although various drugs with different spectra of activity are used in the therapy of epilepsy, they show severe side effects. Furthermore, about 30% of epilepsy patients are refractory to these drugs. Consequently, there is a need for such new antiepileptic drugs, which act via a mechanism different from those in current use. There are great expectations towards those compounds that display their activity by diminishing the glutamate-induced over-activation of the central nervous system (*TIPS*, 15:456 (1994)).

[0060] The anti-seizure activity of some of the compounds of the present invention was measured using the electroshock test (*J. Pharmacol. Exp. Ther.* 106:319 (1952)) and the results are shown in Table 3. The spasmolytic activity of the compounds of the present invention was investigated by using e.g., pentetrazole (*J. Pharmacol. Exp. Ther.* 108:168 (1953)), strychnine (*J. Pharmacol. Exp. Ther.* 129:75 (1960)), bemegrid, nicotine, bicuculline, 4-aminopyridine and mercapto-propionic acid for inducing the clonic-tonic seizures and lethality. The investigated compounds were administered orally in three doses using 10 male CD1 mice/dose, usually 60 min before the induction of seizures. Non-limiting, illustrative results are summarized in Table 3.

Table 3
Investigation of the anticonvulsive activity in mice

Method	Compound (Number of example) / ED_{50} mg/kg po.							
	GYKI 52466	GYKI 53773	61	69	86	84	89	102
MES	37.4	8.6	13.1	14.7	6.1	12.5	10.5	13.9
MES 30'	21.9	4.9	11.5	8.7	4.3	10-15	-	-
Pentetrazol	119.8	16.8	32.5	46.9	10.0	17.1	11.5	35.7
Strychnine	86.7	17.4	35.4	27.7	10.6	18.2	15.7	26.7
Bemegride	71.9	23.9	34.4	33.3	11.2	16.7	11.2	27.9
Bicuculline	35.0	14.6	31.0	18.1	4.6	17.0	17.1	25.8
Nicotine	71.8	22.7	59.3	16.8	16.5	77.2	45.9	31.7
4-AP	43.0	8.4	17.6	16.6	10.1	16.6	14.3	20.4
3-MPA	47.0	17.1	11.0	34.2	4.0	6.8	>50	>50

Abbreviations: MES = maximal electroshock seizure; 4-AP = 4-aminopyridine; 3-MPA = 3-mercapto-propionic acid

[0061] The data provided above indicate that the compounds of formula (I) or (II) of the present invention showed significant anticonvulsive activity in all of the eight tests studied. They reveal both a broader spectrum and more significant anticonvulsive efficacy compared to GYKI 52466 and GYKI 53773, both used as reference compounds in the literature. The protective effect displayed against the different convulsion inducing agents predicts favorably for their potential use in the treatment of the different kinds of epilepsy.

Muscle relaxant activity

[0062] Central muscle relaxants are used in such clinical situations when the resting tone of the skeletal muscles is increased as a consequence of a cerebral trauma or due to a chronic neurodegenerative illness, resulting in muscle rigidity or tremor. The muscle spasm is often painful and hinders normal motion.

[0063] The muscle relaxant activity of the compounds of formula (I) or (II) of the present invention was determined in the inclined screen test described by Randall (*J. Pharmacol.*

Exp. Ther. 129:163 (1960)) as well as in the rotarod test (Dunham *et al.*, *J. Am. Pharm. Assoc.* 46:208 (1957)). The compounds were administered in three doses intraperitoneally using 10 CD1-mice/dose. The muscle relaxant activity of the compounds of the present invention was compared to that of the reference compounds GYKI 52466 and GYKI 53773. Representative, non-limiting results are summarized in Table 4. From these data, it is evident, that the muscle relaxant activity of the compounds of the present invention significantly exceeds that of GYKI 53773, which is now in clinical phase-II studies.

Table 4
Muscle relaxant activity in mice

Compound (Number of example)	Inclined screen ED_{50} ip. (mg/kg)	Rotarod ED_{50} ip. (mg/kg)
GYKI 52466 (reference)	47.1	25.1
GYKI 53773 (reference)	13.4	2.3
61	10.7	5.4
69	12.2	1.2
86	3.9	0.8
84	12.8	1.4
89	4.3	1.7
102	14.8	2.9

[0064] The muscle relaxant activity of the compounds of formula (I) or (II) determined in the above tests indicates potential therapeutic use in the treatment of such illnesses in which the increased muscle tone causes problems. Considering their skeletal muscle relaxant and anti-tremor activity (discussed below), the compounds may be useful in the treatment of essential tremor, multiple sclerosis (spasms + tremor) and Parkinson's disease (rigidity + tremor).

The inhibition of focal ischemia

[0065] The focal anti-ischemic activity of the compounds of formula (I) or (II) of the present invention was measured by the "middle cerebral artery occlusion" (MCAO) test (Bartus *Stroke* 11:2265 (1994) and Sydserff *et al.*, *Brit. J. Pharmacol.* 114:1631 (1995)). The blood supply of the left middle cerebral artery of anaesthetized rats was temporarily blocked (60 min) by an

embolus introduced intra-arterially following Halothane anesthesia, without craniotomy, thereafter the perfusion was reestablished by removing the embolus and thus a human "stroke-like" status was triggered in an experimental animal model. After a histological process (TTC staining) 24h later, the infarcted area was determined by a computer assisted scanner program and was compared to the results obtained in a control group treated with the vehicle. Non-limiting, representative results are summarized in Table 5.

Table 5.
Inhibition of focal ischemia in rats

Compound (Number of example)	Dose mg/kg iv. (6x in every 30 min)	Decrease of the infracted area in % compared to that of the control		
		30 min	120 min	180 min
		Time of first treatment after occlusion		
GYKI 52466 HCl (reference)	2		39*	
	5	34*	47**	
GYKI 53773 (reference)	2	47*	49**	26
61	1		63**	16
	2			46*
69	2			28
86	1			35*

- $p<0.05$; ** $p<0.01$; calculated with Dunnett test following ANOVA (Dunnett *J. Amer. Statist. Ass.* 50:1096 (1955))

[0066] The investigated compounds possess a strong neuroprotective activity in this experimental model, which is considered the model of the human stroke. Some of the compounds, *e.g*, those described in Example 61 and 86, show significant activity even when administered 3 h after the occlusion predicting a potential useful clinical application.

Inhibition of autoimmune inflammation

[0067] Multiple sclerosis is a chronic autoimmune inflammation of the central nervous system in which the axonal myelin coat, assuring the safe impulse conduction, is damaged. The oligodendrocytes forming the myelin coat express mainly AMPA/kainate receptors. Thus, the neurodegenerative process is further enhanced by glutamate, the excitatory neurotransmitter, which is released by the activated immune cells in large quantities which expresses its activity through AMPA/kainate receptors thereby damaging myelin oligodendrocytes and axons of neurons (Steinman *Nature Medicine* 6:15 (2000) and Werner *et al., J. Neurol. Transmiss. Suppl.*, 60:

375 (2000)). As a consequence of these processes, at first mild neurological symptoms, such as visual, sensory, balance, motion and urogenital problems develop which become increasingly serious. The therapy of multiple sclerosis is still an unsolved problem despite the intense research being pursued in this field (Bjartmar *et al.*, *Drugs of Today* 38:17 (2002)).

[0068] Muscle spasticity and intention tremor belong to the most severe neurological symptoms of multiple sclerosis (Baker *et al.*, *Nature* 404:84 (2000)). Moderation or cure of these symptoms by a proper therapy would be very important.

[0069] The activity of the 2,3-benzodiazepine derivatives possessing AMPA antagonistic activity was further investigated in an autoimmune encephalomyelitis model (Smith *et al.*, *Nature Medicine*, 6:62 (2000)) in rats, using immunization with guinea pig myelin basic protein (MBP) and complete Freund adjuvant. The compounds were administered intraperitoneally twice a day for 8 days, starting on day 10 after immunization and with an observation period until symptoms were present. 5-15 animals were used in each group. Their weights were 160-180 g (Lewis rats, female) and 180-220 g (Lewis rats, male). The activity of the compounds was determined according to the symptom score values, and compared to those of the control group (see Table 6). Histopathological investigations were carried out on the brain stem, the spinal cord, and the sciatic nerve (Gijbels *et al.*, *J. Clin. Invest.* 94:2177 (1994)) using 5-10 animals/group. Non-limiting, representative results are presented in Table 7.

Table 6.

Effect of 2,3-benzodiazepines possessing AMPA antagonist activity on the clinical symptoms of autoimmune encephalomyelitis in Lewis rats

Compound (Number of example)	Dose (mg/kg ip.)	Neurological symptoms (change compared to controls, %)			
		Female rats		Male rats	
		0-8 day	0-14 day	0-8 day	0-14 day
GYKI 53773	30	-38*	-27	-43*	-29
(reference)	15	-60*	-63**	-8	+7
GYKI 52466	30	-45	-4	-1	-1
(reference)					
86	15	-97**	-85**	-93*	-67
	7.5	-62**	-66**	-65**	-70**
	3.75	-3	-18	-70**	-77**
	1.875	-40*	-39*	+5	-8
61	7.5	-56*	-53*	-60*	-63**
	3.75	-44	-48	-44*	-46*
	1.875	-18	-7	+13	+5
69	7.5	-29	-24	-51*	-50*
	3.75	+43	+58*	+35	-40*

o $p<0.05$; ** $p<0.01$ (Mann-Whitney test)

Table 7.

Effect of 2,3-benzodiazepine derivatives possessing AMPA antagonistic character on the histological and clinical symptoms of autoimmune encephalomyelitis in Lewis rats on day 24 after immunization.

Compound (Number of example)	Dose (mg/kg ip.)	Histological symptoms (change, %)		Neurological symptoms (change, %)	
		rats		rats	
		Male	female	male	female
GYKI 53773 (reference)	30	+34	-16	-26	-41
86	15	-66	-53	-67	-85
	7.5	+1	-22	-66	-62
	3.75	+4	-20	-72	-21
	1.875	-25	-15	+54	-42
61	7.5	-20	-5	-54	-53

[0070] According to our histopathological and pharmacological investigations the compounds described in, for example, Example 86 and 61 proved to be more active than the reference compound GYKI 53773.

[0071] The anti-tremor effect of the 2,3-benzodiazepine derivatives of the present invention, possessing AMPA antagonistic character in mouse models was studied using three tremorigen agents of different mechanism of action, such as oxotremorine (Rathbun *et al.*, *Psychopharmacology*, 4:114 (1963)), GYKI 20039 (3-(2,6-dichlorophenyl)-2-imino-thiazolidine; (Andrási *et al.*, *Acta Physiol. Acad. Sci. Hung.* 37:183 (1970)) and harmaline. Number of animals: 5/group. Weight of animals: 20-25 g (CD1 mice, male). The activity of the investigated compounds was determined by their score values compared to those of the control group. The ED_{50} values were calculated according to the Litchfield-Wilcoxon method and are listed in Table 8.

Table 8.

Effect of 2,3-benzodiazepine derivatives possessing AMPA antagonistic character on the tremor of CD1 mice induced by different chemical agents.

Compound (Number of example)	Dose range (mg/kg p.o.)	ED_{50} (mg/kg po.)		
		Oxotremorin 1 mg/kg ip.	GYKI 20039 10 mg/kg ip.	Harmaline 40 mg/kg ip.
GYKI 52466 (reference)	6.25-75.0	20.5(14.9-28.3)	37.1(25.2-54.7)	38.5(25.7-57.9)
GYKI 53773 (reference)	3.125-20.0	5.6(3.6-8.5)	10.6(7.2-15.5)	9.0(-7.4-10.9)
86	3.125-9.0	4.3(3.5-5.4)	6.8(5.5-8.5)	6.0(4.9-7.4)

[0073] According to our investigations, the compound described in Example 86 was more active than the reference compounds GYKI 53773 and GYKI 52466, respectively.

[0074] The 2,3-benzodiazepine derivatives with AMPA antagonistic character, compensating for the harmful effect of glutamate by blocking the corresponding receptors, are therapeutically important. Their combined neuroprotective, muscle relaxant, tremor inhibiting etc. properties beneficially influence the progression of the pathological neurological disorders and diminish the pathological neurological symptoms, respectively.

The effect of the compounds of the present invention on the acute and chronic inflammatory disorders of the airways

Bronchial hyperresponsiveness (BHR) and airway eosinophilia (AEP) are characteristic features of bronchial asthma. BHR is typified by an exaggerated response to a wide variety of stimuli that can induce an increased resistance to airflow in the airways. AEP is a result of prolonged eosinophil infiltration, mast cell, and T cell activation in the airways. In actively (*e.g.*, ovalbumin) immunized rats (*e.g.*, Brown Norway [BN] strain), repeated sensitization followed by antigenic challenge results in lung eosinophilia and bronchial hyperresponsiveness to different spasmogens

(*e.g.*, acetylcholine). This is the most frequently employed model for studying potential anti-asthmatic effects of new chemical entities.

[0075] BN rats were actively immunized with allergen (ovalbumin). On day one, rats were sensitized with the subcutaneous administration of ovalbumin suspended in $Al(OH)_3$ (2.5 μg ovalbumin + 20 mg $Al(OH)_3$ in 0.5 ml saline). Booster injections (same dose and same route) were given at day 14 and 21. Simultaneously at each occasion 0.25 ml of *Bordatella pertussis* vaccine was injected intraperitoneally. On day 28, animals were challenged by inhalation of the antigen (vaporized 1% OVA solution for 1 hour). Test compounds were administered orally 2 hours pre-challenge.

[0076] 48 hours following challenge, they were sacrificed by an overdose of urethane (4-5 ml of 15% urethane given i.p.), bronchoalveolar lavage fluid (BALF) was obtained, and tracheae dissected from the animals. Eosinophil cell count (cells/ml BALF) was determined manually using a selective stain for eosinophils and counting the cells in a Buerker chamber. BHR was determined using tracheal rings suspended in an organ bath. After an equilibration period of 30 minutes, cumulative concentration response curves to acetylcholine were determined. Maximal response of control (unchallenged, non-treated) tracheal rings is obtained at 10^{-3} M acetylcholine. The height of this response is defined as 100%. All other contractions are expressed as a percentage and related to the control response.

Results

Table 9.

Effect of GYKI 52466 (reference), GYKI 53773 (reference) and the compound described in Example 86 on the bronchial hypersensitivity and the eosinophilia of the airways on BN-rats sensitized with ovalbumin and antigen challenged by inhalation (mean±SE, p determined by Student's t-test).

				Compound (Number of example)
Experiment	Parameter	Control	Challenge	**GYKI 52466** (reference) 3.0 mg/kg po
1	ED_{50}*	5.63±0.46	6.74±1.45	5.60±1.53
	p	*0.002*		*0.028*
	MAX**	100±0	276±217	135±105
	p	*0.001*		*0.037*
	Eosinophil***	0.17±0.01	1.24±0.23	0.91±0.13
	p	*0.010*		*NS*[t]
Experiment	Parameter	Control	Challenge	**GYKI 53773** (reference) 3.0 mg/kg po
2	ED_{50}*	5.22±0.59	5.89±0.66	4.64±0.91
	p	*0.003*		*0.001*
	MAX**	100±0	163±65	85±43
	p	*<0.001*		*0.007*
	Eosinophil***	0.38±0.11	1.24±0.13	1.29±0.11
	p	*0.004*		*NS*[t]
Experiment	Parameter	Control	Challenge	**86** 3.0 mg/kg po
3	ED_{50}*	5.78±0.17	6.99±0.32	4.95±0.59

p	*0.001*		*0.008*
MAX**	100±0	255±50	81±14
p	*0.001*		*0.003*
Eosinophil***	0.23±0.08	1.43±0.27	1.32±0.32
p	*0.005*		*NS*[t]

- acetylcholine (Ach) concentration (-log M) which causes a 50% contraction compared to the control

** relative contraction compared to the control at a maximal Ach concentration

*** BALF eosinophil number ($x10^6$/ml)

[t] not significant ($p > 0.05$)

[0077] The representative results presented in Table 9 show that representative compounds according to the present invention diminished the bronchial hyperresponsiveness caused by the allergen. The eosinophilia was not significantly influenced by the applied doses.

[0078] The results of the different pharmacological investigations mentioned above show that the compounds of formula (I) or (II) of this invention are able to beneficially influence various diseases and disorders in which glutamate (AMPA/kainate) receptors have been implicated. Consequently the compounds according to the invention are suitable for treating neurological and psychiatric disorders, triggered by the extremely enhanced activity of the AMPA receptor. Therefore, they have therapeutic utility as anticonvulsants, muscle relaxants, as well as neuroprotective agents. They also display therapeutic value for the treatment of epilepsy, as well as different illnesses in which the spasm of skeletal-muscles is involved, and in the treatment of neurodegenerative disorders such as *e.g.*, cerebral ischemia (stroke).

[0079] Exemplary neurological illnesses which can be beneficially influenced or prevented include Parkinson's disease, Alzheimer's disease, Huntington chorea, amyotrophic lateral sclerosis, olivopontocerebellaric atrophy, AIDS dementia, senile dementia. A similar beneficial effect can be achieved in the treatment of neurodegenerative processes caused by cerebrovascular catastrophe (stroke, brain, and spinal injuries) or hypoxia, anoxia or hypoglycemia. The compounds of the invention can be advantageously used for the treatment of different psychiatric diseases such as anxiety, schizophrenia, sleep disorders, as well as

alleviating the withdrawal syndrome of alcohol and drug abuse. Furthermore they may inhibit tolerance development in the case of sedatives or analgesics.

[0080] It can be expected that they can be advantageously used in epileptic disease entities, in the cure or palliation of muscle spasms of central origin and in the relief of pathologic pain as well as in the treatment of urinary incontinence.

[0081] In one aspect of the invention, a method of blocking the activation of one or more excitatory amino acid receptors in mammals is provided. This method includes administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound of the formula (I) or (II).

[0082] In another aspect of the invention, a method of treating epilepsy in mammals is provided. This method includes administering to a mammal in need of such treatment an antiepileptic amount of a compound of the formula (I) or (II).

[0083] In another aspect of the invention, a method of treating spasms of the skeletal musculature in mammals is provided. This method includes administering to a mammal in need of such treatment a muscle-relaxing amount of a compound of the formula (I) or (II).

[0084] In still another aspect of the invention, a method of treating acute and chronic neurodegenerative disorders in mammals is provided. This method includes administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound of the formula (I) or (II).

[0085] In yet another aspect of the invention, a method for treating inflammatory disorders in mammals is provided. This method includes administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound of the formula (I) or (II).

[0086] In other aspects of the invention, the compounds of formula (I) or (II) can be advantageously used in the treatment of multiple sclerosis. A further therapeutic field, in which the compounds of formula (I) or (II) can be used, are illnesses that are caused by the over-function of the periferic glutamate receptors. Such illnesses include the acute and chronic inflammatory disorders of the airways particularly allergic inflammations such as asthma-related pathologies. This latter potential therapeutic use is supported by the results obtained in ovalbumin sensitized rats.

[0087] In one aspect of the invention, a pharmaceutical composition is provided including a compound of formula (I) or (II), or a stereoisomer, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, excipient or diluent.

[0088] The compounds of formula (I) or (II) are formulated in a pharmaceutically acceptable vehicle with any of the well-known pharmaceutically acceptable carriers, including diluents and excipients (see Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, Mack Publishing Co., Easton, PA 1990 and Remington: The Science and Practice of Pharmacy, Lippincott, Williams & Wilkins, 1995). While the type of pharmaceutically acceptable carrier/vehicle employed in generating the compositions of the invention will vary depending upon the mode of administration of the composition to a mammal, generally pharmaceutically acceptable carriers are physiologically inert and non-toxic. Formulations of pharmaceutical compositions may contain more than one type of compound of formula (I) or (II), as well as any other pharmacologically active ingredient useful for the treatment of the particular conditions, disease, or symptom being treated.

[0089] The compositions of the invention can be administered by standard routes (*e.g.*, oral, inhalation, rectal, nasal, topical, including buccal and sublingual, or parenteral, including subcutaneous, intramuscular, intravenous, intradermal, transdermal, and intratracheal). In addition, polymers may be added according to standard methodologies in the art for sustained release of a given compound.

[0090] For oral administration, the compositions of the invention may be presented as discrete units such as capsules, caplets, gelcaps, cachets, pills, or tablets each containing a predetermined amount of the active ingredient as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, *etc.* Alternately, administration of a composition including the compound of formula (I) or (II) may be effected by liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems.

[0091] Formulations suitable for administration by inhalation include formulations that can be dispensed by inhalation devices known to those in the art. Such formulations may include carriers such as powder and aerosols. Liquid and powdered compositions suitable for nebulization and intrabronchial use, or aerosol compositions administered via an aerosol unit dispensing metered doses ("MDI") are contemplated.

[0092] The active ingredient may be formulated in an aqueous pharmaceutically acceptable inhalant vehicle, such as, for example, isotonic saline or bacterostatic water and other types of vehicles that are well known in the art. The solutions are administered by means of a pump or squeeze-actuated nebulized spray dispenser, or by any other conventional means for causing or enabling the requisite dosage amount of the liquid composition to be inhaled into the patient's lungs.

[0093] Powder compositions include, by way of illustration, pharmaceutically acceptable powdered preparations of the active ingredient thoroughly intermixed with lactose or other inert powders acceptable for intrabronchial administration. The powder compositions can be administered via a dispenser, including, but not limited to, an aerosol dispenser or encased in a breakable capsule, which may be inserted by the patient into a device that punctures the capsule and blows the powder out in a steady stream.

[0094] Aerosol formulations for use in the subject method typically include propellants, surfactants, and co-solvents and may be filled into conventional aerosol containers that are closed by a suitable metering valve.

[0095] Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of 20 to 500 microns which is administered in the manner in which snuff is administered, *i.e.* by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations, wherein the carrier is a liquid, for administration, for example via a nasal spray, aerosol, or as nasal drops, include aqueous or oily solutions of the compound of formula (I) or (II).

[0096] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, stabilizers, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

[0097] The dosage of the active ingredient depends on the route of administration, the type and severity of the disease as well as the weight and age of the patient. The daily dose for

adult patients can be 0.1-500 mg, preferably 1-100 mg, in a single dose or divided in several doses.

[0098] In another aspect of the present invention, a method is provided for treating (a) an acute or chronic neurodegenerative disease associated with glutamate dysfunction; (b) a method for treating epilepsy; (c) a method for reducing muscle spasm in mammals; (d) a method for preventing, treating or alleviating the symptoms of acute or chronic inflammatory disorders of the airways; (e) a method for relief of pathological pain in mammals. These methods include administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or (II).

[0099] The term "therapeutically effective amount" is used to denote treatments at dosages effective to achieve the therapeutic result sought. Furthermore, one of skill will appreciate that the therapeutically effective amount of the compound of the invention may be lowered or increased by fine-tuning and/or by administering more than one compound of the invention, or by administering a compound of the invention with another pharmacologically active compound. The invention therefore provides a method to tailor the administration/treatment to the particular exigencies specific to a given mammal. As illustrated in the following examples, therapeutically effective amounts may be easily determined for example empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect.

[00100] It will be appreciated by those of skill in the art that the number of administrations of the compounds according to the invention will vary from patient to patient based on the particular medical status of that patient at any given time.

[00101] The compounds according to the invention and the process for their preparation are illustrated in detail by the following Examples.

[00102] The following examples are intended to further illustrate certain preferred embodiments of the invention and are not limiting in nature. Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific substances and procedures described herein.

EXAMPLES

[00103] The starting materials of the examples were synthesized as follows:

(±)-8-Methyl-5-(4-nitrophenyl)-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (I)

[00104] A mixture of 0.90 g (9.26 mmol) of potassium thiocyanate, 2.00 g (6.15 mmol) of (±)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine and 40 ml of acetic acid was stirred at 100-110°C for 6 h. After cooling, the precipitated crystals were filtered off, washed with water and dried to yield 1.80 g (76%) of the title compound. Mp.: 242-243°C.

[00105] The thiocarbamoyl compounds II-X were synthesized from the corresponding dihydro-[2,3]benzodiazepine according to the above procedure.

(R)-8-Methyl-5-(4-nitrophenyl)-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (II)

[00106] Mp.: 213-215 °C. Yield: 73 %, $[\alpha]_D$: -251° (c=0.5; $CHCl_3$).

(S)-8-Methyl-5-(4-nitrophenyl)-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (III)

[00107] Mp.: 213-214 °C. Yield: 76 %, $[\alpha]_D$: +252° (c=1; $CHCl_3$).

(±)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (IV)

[00108] Mp.: 230-236 °C. Yield: 86 %.

(±)-8-Chloro-4-methyl-(4-nitrophenyl)-3-thiocarbamoyl-4,5-dihydro-3H-[2,3]benzodiazepine (V)

[00109] Mp.: 261-265°C. Yield: 72%.

(±)-7,8-Dichloro-4-methyl-1-(4-nitrophenyl)-3-thiocarbamoyl-4,5-dihydro-3H-[2,3]benzodiazepine(VI)

[00110] Mp.: amorphous. Yield: 59%.

(±)-8-Methyl-5-phenyl-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (VII)

[00111] Mp.: 225-235°C. Yield: 86%.

5-(4-Nitrophenyl)-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (VIII)

[00112] Mp.: 235-238°C. Yield: 62%.

(±)-8-Methyl-5-(4-methyl-3-nitrophenyl)-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (IX)

[00113] Mp.: 201-202°C. Yield: 84%.

(±)-7-Bromo-4-methyl-8-methoxy-1-(4-nitrophenyl)-3-thiocarbamoyl-3,4-dihydro-3H-[2,3]benzodiazepine (X)

[00114] Mp.: 250-253°C. Yield: 94%.

(±)-8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl chloride (XI)

[00115] 3.25 g (10.0 mmol) of (±)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine was dissolved in 90 ml of dry toluene by warming and after adding 2.17 ml (15.5 mmol) of triethylamine, was reacted with 1.90 ml (15.0 mmol) of trimethylsilyl chloride at about 28-30°C. After stirring at room temperature for 16 h this reaction mixture was added dropwise over a period of about 2 h to the solution of 1.38 g (12.0 mmol) of thiophosgene in 30 ml of dry toluene. This mixture was stirred at room temperature for 5 h, and then diluted with 30 ml of toluene. It was then decomposed by addition of 30 ml of water. After separation, the toluene phase was washed twice with 30 ml of water, followed by a 10% aqueous sodium chloride solution. After drying, the solvent was evaporated and the residue was treated with diisopropyl ether to yield 3.27 g (81%) of the crude product.

[00116] The crude product was recrystallized from chloroform, petroleum ether.

[00117] Yield: 3.05 g. Mp.: about 185°C it recrystallizes, then it melts at 210°C.

[00118] The carbothioyl chloride type compounds XII-XVII were synthesized by analogous methods from racemic or optically active dihydro-[2,3]benzodiazepine derivatives:

(R)-8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl chloride (XII)

[00119] Mp.: 187-188°C. Yield: 80%, $[\alpha]_D$: -610° (c=0.5; $CHCl_3$).

(±)-8-Methyl-5-(3-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl chloride (XIII)

[00120] Mp.: 198-199°C. Yield: 79%.

(±)-8-Methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl chloride (XIV)

[00121] Mp.: 210-215 °C. Yield: 79 %.

(±)-8-Methyl-5-(4-methyl-3-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h] [2,3]benzodiazepine-7-carbothioyl chloride (XV)

[00122] Mp.: 201-202 °C. Yield: 84 %.

(±)-8-Chloro-4-methyl-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine-3-carbothioyl chloride (XVI)

[00123] Mp.: 210-214°C (DMF). Yield: 70%.

(±)-7-Bromo-4-methyl-8-methoxy-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine-3-carbothioyl chloride (XVII)

[00124] Mp.: 199-204°C. Yield: 82%.

(±)-8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothiohydrazide (XVIII)

[00125] 1.0g (2.47 mmol) of carbothioyl chloride XI was added to a stirred solution of 0.37 g (7.42 mmol) of hydrazine hydrate in 15 ml of tetrahydrofuran at 5-10 °C over a period of about 0.5 h, then after 1 h stirring, the mixture was poured into water and the precipitated product was filtered off to yield 0.89 g (90 %) of the crude product. After drying, it was used in the further reaction steps. The melting point of the product after recrystallization from ethanol was 196 °C.

[00126] The carbothiohydrazide derivatives XIX-XXII were synthesized by analogous methods:

(R)-8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothiohydrazide (XIX)

[00127] Mp.: 140-142 °C. Yield: 99 %, $[\alpha]_D$: -201° (c=0.5; $CHCl_3$).

(±)-8-Chloro-4-methyl-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine-3-carbothiohydrazide (XX)

[00128] Mp.: 210-211 °C. Yield: 61 %.

(±)-7-Bromo-4-methyl-8-methoxy-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine-3-carbothiohydrazide (XXI)

[00129] Mp.: 196-201°C. Yield: 98%.

(±)-8-Methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothiohidrazide (XXII)

[00130] Mp.: 188-190°C. Yield: 98%.

(±)-8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbonitrile (XXIII)

[00131] A mixture of 3.25 g (10 mmol) of (±)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine, 20 ml of dimethylformamide, 2.76 g (20 mmol) of potassium chloride and 1.80 g (17 mmol) of cyanogen bromide was stirred at room temperature

for 20 h. After pouring into water, the precipitated crystals were filtered off, and washed with water to yield 3.34 g (95%) of the title compound, Mp.: 172-176 °C.

(±)-8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbamidoxime (XXIV)

[00132] A mixture of 2.80 g (8.0 mmol) of compound XXIII, 30 ml of 2-methoxyethanol, 0.84 g (10 mmol) of sodium acetate and 0.60 g (8.8 mmol) of hydroxylamine hydrochloride was stirred for 0.5 h, then concentrated in vacuum. The residue was treated with water, the precipitated crystals were filtered off and washed with water to yield 3.05 g (100%) of the title compound, Mp.: 138-145°C.

(±)-8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carboxylic acid (2-chloroethyl)-amide (XXV)

[00133] A mixture of 1.0 g (3.07 mmol) of (±)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine, 25 ml of dry dichloromethane and 0.62 g (5.88 mmol) of 2-chloroethyl isocyanate was stirred at room temperature for 24 h, then concentrated. The residue was purified by refluxing in ethanol to yield 1.25 g (94%) of the title compound, Mp.: 222-223°C.

(±)-Phenyl (8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo [4,5-h][2,3]benzodiazepine-3-carbothioyl)-carbamate (XXVI)

[00134] 0.37 g (3.80 mmol) of potassium thiocyanate was dissolved in 8 ml of acetone, then 0.48 ml (3.80 mmol) of phenyl chloroformate was added dropwise to the mixture at room temperature. The reaction mixture was stirred at room temperature for 0.5 h, then at 40°C for 0.25 h. Then the mixture was cooled with ice-water and a solution of 1.04 g (3.20 mmol) of (±)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine in 15 ml of acetone was added dropwise over a period of 0.5 h. After stirring for 0.5 h the bulk of the solvent was evaporated and the residue was treated with water, the crystals were filtered and washed with water to yield 1.73 g, (90%) of the title compound. Mp.: 160°C.

(±)-1-Methyl-3-{8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl}-urea (XXVII)

[00135] 1.57 g (3.11 mmol) of compound XXVI was dissolved in 8 ml of dimethylformamide and 0.35 ml (4.04 mmol) of 40% aqueous methylamine solution was added dropwise to the ice cooled stirred solution. After stirring for 2 h the mixture was poured into water, the precipitated crystals were filtered off and washed with water to yield 1.56 g of the crude product, which was recrystallized from ethanol. Yield: 1.01 g (73%). Mp.: 192-193°C.

[00136] The compounds XXVIII and XXIX were synthesized analogously.

(±)-1-Cyclopropyl-3-{8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl}-urea (XXVIII)

[00137] Mp.: 281-283°C (ethyl acetate). Yield: 80%

(±)-1-Ethyl-3-{8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl}-urea (XXIX)

[00138] Mp.: 176-177°C (methanol). Yield: 73%.

(±)-1-{8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl}-4-methyl-semicarbazide (XXX)

[00139] To a stirred solution of 0.40 g (1.0 mmol) of compound XVIII in 15 ml of chloroform 0.07 ml (1.2 mmol) of methyl isocyanate was added. After 1 h the reaction mixture was washed with sodium hydrogen carbonate solution and water and after concentration the obtained solid material was purified by refluxing in ethanol. The desired product was 0.36 g, yield: 88%. Mp.: 200°C.

(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h]

[2,3]benzodiazepine (XXXI)

[00140] The title compound was prepared based on the procedures described in the literature (Ling *et al., J. Chem Soc. Perkin Trans.* 1:1423 (1995)) and the British patent specification No. 2,311,779.

[00141] Mp.: 159-160°C (ethanol). $[\alpha]_D$: +172° (c=1; $CHCl_3$).

(R)-7-(tert-Butoxycarbonyl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (XXXII)

[00142] The compound was prepared according to a synthesis described in literature (Anderson *et al., J. Am Chem Soc* 117: 12358(1995)) with the exception that tert-butyl carbazate was used instead of acetic hydrazide.

[00143] Mp.: 168-169°C (isopropanol). $[\alpha]_D$: -444° (c=0.6; $CHCl_3$).

Example 1

(±)-8-Methyl-5-(4-nitrophenyl)-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00144] A mixture of 1.00 g (2.60 mmol) of the starting material I, 2.54 g (12.89 mmol) of bromoacetaldehyde diethyl acetal and 10 ml of dimethylformamide was stirred at 80°C for 40 min. Then the reaction mixture was diluted with water and the crude product obtained was recrystallized from ethanol to yield 0.85 g (80%) of the title compound. Mp.: 145-150°C.

Example 2

(R)-8-Methyl-5-(4-nitrophenyl)-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00145] The title compound was obtained from the starting material II according to the method described in Example 1. Mp.: 108-110°C, yield: 89%, $[\alpha]_D$: +514° (c=0.5; $CHCl_3$)

Example 3

(S)-8-Methyl-5-(4-nitrophenyl)-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00146] The title compound was obtained from the starting material III according to the method described in Example 1. Mp.: 114-116°C, yield: 83%, $[\alpha]_D$: -522° (c=0.6; $CHCl_3$)

Example 4

(±)-8-Methyl-7-(4-methyl-thiazol-2-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00147] A mixture of 0.76 g (1.98 mmol) of the starting material I, 1.10 g (11.88 mmol) of chloroacetone and 15 ml of dimethylformamide was stirred at 80-90°C for 40 min. Then the

reaction mixture was diluted with water, the precipitated crystals were filtered off, dried and purified by refluxing in ethanol to yield 0.69 g (82%) of the title compound; Mp.: 188-189°C.

Example 5

(±)-8-Methyl-7-(5-methyl-thiazol-2-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00149] A mixture of 1.50 g (3.90 mmol) of starting material I, 3.57 g (19.50 mmol) of 2-bromopropionaldehyde dimethyl acetal and 15 ml of dimethylformamide was stirred at 90°C for 1.5 h. Then the reaction mixture was diluted with water and the crude product obtained was purified by column chromatography using silica gel (MN Kieselgel 60; Macherey-Nagel, Düren, Germany) as adsorbent and a mixture of toluene – ethyl acetate (16:1) as eluent to yield 1.08 g (66%) of the title compound; Mp.: 193-195°C.

Example 6

(±)-7-(4,5-Dimethyl-thiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00150] A mixture of 0.60 g (1.56 mmol) of the starting material I, 1.02 g (9.57 mmol) of 3-chloro-2-butanone and 8 ml of dimethylformamide was stirred at 90°C for 3 h. After cooling the precipitated crystals were filtered off, dried and purified by recrystallization from dimethylformamide and water to yield 0.49 g (76%) of the title compound; Mp.: >260 °C (dec.).

Example 7

(±)-8-Methyl-5-(4-nitrophenyl)-7-(4-phenyl-thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00151] A mixture of 0.45 g (1.17 mmol) of the starting material I, 0.35 g (1.76 mmol) of phenacyl bromide and 7 ml of dimethylformamide was stirred at 80°C for 30 min. After cooling the precipitated crystals were filtered off, washed with ethanol and dried to yield 0.50 g (88%) of the title compound; Mp.: >260 °C (dec.).

Example 8

(±)-7-(4-Ethoxycarbonyl-thiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00152] A mixture of 0.45 g (1.17 mmol) of the starting material I, 0.46 g (2.36 mmol) of ethyl bromopyruvate and 7 ml of dimethylformamide was stirred at 80°C for 30 min. After cooling the precipitated crystals were filtered off, washed with ethanol and dried to yield 0.41 g (85%) of the title compound; Mp.: 242-243°C.

Example 9

(±)-7-(4,5-Dihydro-thiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00153] A mixture of 1.00 g (2.6 mmol) of the starting material I, 2.13 g (10.40 mmol) of 2-bromoethylamine hydrobromide and 10 ml of dimethylformamide was stirred at 90-100°C for 4 h. After diluting with water the precipitated crystals were filtered off, dissolved in dichloromethane and washed several times with 10% sodium hydrogen carbonate solution. After drying the product was purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of hexane – ethyl acetate (1:1) as eluent to yield 0.80 g (75%) of the title compound; Mp.: 185-187°C.

Example 10

(R)-7-(4,5-Dihydro-thiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00154] The title compound was obtained from the starting material II according to the method described in Example 9.

[00155] Mp.: 118-124°C. Yield: 73%, $[\alpha]_D$: +575° (c=0.4; $CHCl_3$).

Example 11

(S)-7-(4,5-Dihydro-thiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00156] The title compound was obtained from the starting material III according to the method described in Example 9.

[00157] Mp.: 120-125°C. Yield: 71%. $[\alpha]_D$: -594° (c=0.4; $CHCl_3$).

Example 12

(±)-7-(4,5-Dihydro-4-oxo-thiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00158] A mixture of 1.00 g (2.6 mmol) of the starting material I, 1.19 g (7.78 mmol) of methyl bromoacetate and 10 ml of dimethylformamide was stirred at 80-90°C for 1 h. After diluting with water the obtained crude product was purified by refluxing in methanol to yield 1.00 g (91%) of the title compound; Mp.: 218-220°C.

Example 13

(±)-7-(4,5-Dihydro-5-methyl-4-oxo-thiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00159] A mixture of 1.00 g (2.60 mmol) of the starting material I, 0.94 g (5.19 mmol) of ethyl 2-bromopropionate and 10 ml of dimethylformamide was stirred at 80-90°C for 2 h. After diluting with water the obtained crude product was purified by refluxing in 15 ml of ethanol to yield 1.08 g (95%) of the title compound; Mp.: 213-214°C.

Example 14

(±)-7-(5,6-Dihydro-4-oxo-4H-1,3-thiazin-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00160] A mixture of 2.00 g (5.20 mmol) of the starting material I, 1.89 g (10.44 mmol) of ethyl 3-bromopropionate and 20 ml of dimethylformamide was stirred at 80-90°C for 3 h. The reaction mixture was diluted with 25% sodium chloride solution and extracted with dichloromethane. After drying and concentration the crude product was purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of ethyl acetate - methanol (2:1) as eluent to yield 1.34 g (59%) of the title compound; Mp.: 220-221°C.

Example 15

5-(4-Nitrophenyl)-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00161] The title compound was obtained from the starting material VIII and bromoacetaldehyde diethyl acetal according to the method described in Example 1. Mp.: 203-215°C. Yield: 77%.

Example 16

(±)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00162] The title compound was obtained from the starting material IV according to the method described in Example 1. Mp.: 171-175°C. Yield: 46%.

Example 17

(±)-8-Methyl-5-phenyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00163] The title compound was obtained from the starting material VII according to the method described in Example 1. Mp.: 180-184°C. Yield: 51%.

Example 18

(±)-7-Bromo-4-methyl-8-methoxy-1-(4-nitrophenyl)-3-(2-thiazolyl)-4,5-dihydro-3H-[2,3]benzodiazepine

[00164] The title compound was obtained from the starting material X according to the method described in Example 1. Mp.: 184-190°C. Yield: 54%.

Example 19

(±)-8-Chloro-4-methyl-1-(4-nitrophenyl)-3-(2-thiazolyl)-4,5-dihydro-3H-[2,3]benzodiazepine

[00165] The title compound was obtained from the starting material V according to the method described in Example 1. Mp.: 213-216°C. Yield: 67%.

Example 20

(±)-8-Chloro-4-methyl-3-(4-methyl-thiazol-2-yl)-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine

[00166] The title compound was obtained from the starting material V according to the method described in Example 4. Mp.: 209-216°C. Yield: 94%.

Example 21

(±)-3-(4,5-Dihydro-thiazol-2-yl)-8-chloro-4-methyl-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine

[00167] The title compound was obtained from the starting material V according to the method described in Example 9. Mp.: 225-227°C. Yield: 69%.

Example 22

(±)-3-(4,5-Dihydro-3-oxo-thiazol-2-yl)-8-chloro-4-methyl-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine

[00168] The title compound was obtained from the starting material V according to the method described in Example 12. Mp.: 226-228°C. Yield: 96%.

Example 23

(±)-7,8-Dichloro-4-methyl-3-(4-methyl-thiazol-2-yl)-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine

[00169] The title compound was obtained from the starting material VI according to the method described in Example 4. Mp.: 240-242°C. Yield: 77%.

Example 24

(±)-7-(4,5-Dihydro-oxazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00170] A mixture of 1.43 g (3.32 mmol) of the starting material XXV, 1.38 g (9.98 mmol) of anhydrous potassium carbonate, 0.24 g (1.60 mmol) of sodium iodide and 24 ml of dimethylformamide was stirred at 100-110°C for 4 h. Then the mixture was diluted with water and the precipitated crude product was recrystallized from ethanol to yield 1.00 g (76%) of the title compound; Mp.: 194-196°C.

Example 25

(±)-8-Methyl-5-(4-nitrophenyl)-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00171] A mixture of 0.57 g (1.43 mmol) of the starting material XVIII, 6 ml of triethyl orthoformate and a catalytic amount of hydrochloric acid was stirred at 80°C for 1 h. After

cooling the precipitated crystals were filtered off, washed with ethanol and dried to yield 0.45 g (77%) of the title compound; Mp.: 212-213°C.

Example 26

(R)-8-Methyl-5-(4-nitrophenyl)-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00172] The title compound was obtained from the starting material XIX according to the method described in Example 25. Mp.: 144-147°C (ethanol - water). Yield: 88%, $[\alpha]_D$: +428° (c=0.2; $CHCl_3$)

Example 27

(±)-8-Methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00173] To an ice cooled stirred mixture of 1.0 g (2.50 mmol) of the starting material XVIII, 35 ml of dichloromethane, 0.40 ml (2.75 mmol) of triethylamine and 0.22 ml (2.80 mmol) of acetyl chloride was added. The so obtained solution was left at room temperature for 16 h, then 0.6 g of p-toluenesulfonic acid was added and the mixture was stirred at 40°C for 2 h. Then the reaction mixture was washed with sodium hydrogen carbonate solution and water until neutrality, dried and concentrated. The crude product was treated with methanol, then recrystallized from ethanol to yield 0.99 g (91%) of the title compound. Mp.: 213-215°C.

Example 28

(R)-8-Methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Method A.

[00174] The title compound was obtained from the starting material XIX by carrying out the acylation with acetic anhydride according to the method described in Example 27. The obtained crude product was purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of n-hexane – ethyl acetate (1:1) as eluent. After concentration of the fractions containing the title compound, the residue was treated with isopropyl ether to yield 0.95 g of a solid foam (polymorph). Yield: 89%.

Method B.

[00175] To a solution of 4.04 g (10.0 mmol) of the starting material XII, 3 ml of dimethylformamide, 1.40 ml (10.0 mmol) of triethylamine and 0.06 g (0.5 mmol) of 4-dimethylaminopyridine 1.48 g (20.0 mmol) of acetic hydrazide was added. The reaction mixture was stirred at 50°C for 5 h, then diluted with water, the precipitated crystals were filtered off and washed with water. The so obtained 4.5 g of (R)-N'-{8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl}-acetic hydrazide according to its ^{1}H-NMR spectrum was a mixture of rotation isomers. (The analyzed sample was purified by column chromatography using a mixture of n-hexane – ethyl acetate (1:1) as eluent and it was crystallized with 0.5 mol of ethyl acetate, Mp.: 118°C).

[00176] To a suspension of the above intermediate in 50 ml of ethanol 0.75 ml of concentrated hydrochloric acid was added, and the so obtained solution was refluxed for 2 h. After concentration and treatment with water 4.2 g of a crude product was obtained. Purification by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of n-hexane – ethyl acetate as eluent and drying at 60°C in vacuum yielded the title compound with a melting point of 101-102°C. $[\alpha]_D$: +453° (c=0.5; $CHCl_3$).

[00177] The compounds of Examples 29-34 were obtained according to the method described in Example 27 using the appropriate acid chlorides.

Example 29

(±)-7-(5-Cyclopropyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00178] Mp.: 142-145°C; yield: 49%.

Example 30

(±)-7-(5-Ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00179] Mp.: 163-164°C; yield: 84%.

Example 31

(R)-7-(5-Ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00180] Mp.: 105°C; yield: 63%. $[\alpha]_D$: +418° (c = 0.5; $CHCl_3$).

Example 32

(±)-8-Methyl-5-(4-nitrophenyl)-7-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00181] Mp.: 184-185°C; yield: 67%.

Example 33

(±)-8-Methyl-5-(4-nitrophenyl)-7-(5-phenyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00182] Mp.: 210-212°C; yield: 56%.

Example 34

(±)-7-(5-Chloromethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00183] Mp.: 210-211°C; yield: 64%.

Example 35

(±)-7-(5-Cyclopropylaminomethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00184] A mixture of 5 ml of dimethylformamide, 0.44 g (0.96 mmol) of (±)-7-(5-chloromethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo

[00185] [4,5-h][2,3]benzodiazepine (Example 34) and 0.37 ml (5.31 mmol) of cyclopropylamine was stirred at 70-80°C for 1 h. Then the reaction mixture was poured into 20% sodium chloride solution and, the precipitated crude product was extracted into ethyl acetate. The solution was washed with water, dried and after evaporation yielded 0.39 g (85%) of the title compound, as solid foam.

Example 36

(±)-8-Chloro-4-methyl-1-(4-nitrophenyl)-3-(1,3,4-thiadiazol-2-yl)-4,5-dihydro-3H-[2,3]benzodiazepine

The title compound was obtained from the starting material XX according to the method described in Example 25. Mp.: 188°C; yield: 86%

Example 37

(±)-8-Chloro-4-methyl-3-(5-methyl-1,3,4-thiadiazol-2-yl)-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine

The title compound was obtained from the starting material XX according to the method described in Example 27. Mp.: 162-164°C; yield: 52%.

Example 38

(±)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00188] The title compound was obtained from the starting material XXII according to the process described in method A of Example 28.

[00189] Mp.: 228-240°C; yield: 74%.

Example 39

(±)-8-Methyl-5-(4-methyl-3-nitrophenyl)-7-(5-methyl-1,3,4-thiadiazol-5-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00190] The title compound was obtained from the starting material XV according to the process described in method B of Example 28.

[00191] Mp.: 220°C (ethanol); yield: 57%.

Example 40

(±)-8-Methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-5-(3-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00192] The title compound was obtained from the starting material XIII according to the process described in method B of Example 28.

[00193] Mp.: 118-119°C; yield: 67%.

Example 41

(±)-7-Bromo-4-methyl-3-(5-methyl-1,3,4-thiadiazol-2-yl)-8-methoxy-1-(4-nitrophenyl)-4,5-dihydro-3H-[2,3]benzodiazepine

[00194] The title compound was obtained from the starting material XXI according to the process described in method A of Example 28.

[00195] Mp.: 229-233°C; yield: 76%.

Example 42

(±)-8-Methyl-7-(5-methyl-6H-1,3,4-thiadiazin-2-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00196] A mixture of 1.00 g (2.50 mmol) of the starting material XVIII, 20 ml of dimethylformamide and 0.57 g (6.16 mmol) of chloroacetone was stirred at room temperature for 2 h. After dilution with water the precipitated crystals were filtered off and purified by refluxing in ethyl acetate to yield 0.73 g (67%) of the title compound; Mp.: 203-204°C.

Example 43

(±)-7-(5,6-Dihydro-5-oxo-4H-1,3,4-thiadiazin-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00197] A mixture of 1.00 g (2.50 mmol) of the starting material XVIII, 20 ml of dimethylformamide and 0.94 g (6.14 mmol) of methyl bromoacetate was stirred at 70°C for 1.5 h. After dilution with water the precipitated crystals were filtered off and purified by refluxing in ethyl acetate to yield 0.41 g (37%) of the title compound; Mp.: 294-295°C (dec.).

Example 44

(±)-8-Methyl-5-(4-nitrophenyl)-7-(5-oxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00198] A mixture of 2.14 g (4.69 mmol) of the starting material XXX and 122 ml of concentrated hydrochloric acid was stirred at 80°C. A solid material precipitated from the starting solution. The reaction mixture was concentrated to about half of its volume, diluted with 40 ml of water and made alkaline with sodium hydrogen carbonate solution. The

precipitated product was filtered off and washed with water to yield 1.40 g (70%) of the title compound. Mp.: 288°C.

Example 45

(R)-8-Methyl-5-(4-nitrophenyl)-7-(5-methyl-1,3,4-oxadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00199] A stirred mixture of 2.2 g (5.15 mmol) of (R)-N'-(8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepin-7-carbothioyl)-acetic hydrazide (an intermediate of method B of Example 28), 44 ml of ethanol and 1.72 g (5.39 mmol) of mercury (II) acetate was refluxed for 2 h. The residue obtained on concentration was dissolved in dichloromethane and filtered through a neutral aluminum oxide column. After washing the column the filtrate was concentrated and the residue was purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of n-hexane – ethyl acetate (1:2.5) as eluent to yield 1.07 g (51%) of the title compound. Mp.: 202-204°C after recrystallization from ethanol. $[\alpha]$: -249° (c=0.22; $CHCl_3$).

Example 46

(±)-8-Methyl-7-(2-methyl-3-oxo-2,3-dihydro-1,2,4-thiadiazol-5-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00200] To an ice cooled stirred solution of 0.44 g (1.0 mmol) of the starting material XXVII in 8 ml of chloroform a solution of 0.19 g (1.2 mmol) of bromine in 3 ml of chloroform was added. After 0.5 h the reaction mixture was diluted with 15 ml of chloroform and washed with sodium hydrogen carbonate solution and water. The residue obtained on concentration was stirred with methanol and filtered to yield 0.36 g (82%) of the title compound. Mp.: 296°C after recrystallization from ethyl acetate.

[00201] The compounds of Example 47 and 48 were obtained analogously from the starting materials XXVIII and XXIX, respectively.

Example 47

(±)-7-(2-Cyclopropyl-3-oxo-2,3-dihydro-1,2,4-thiadiazol-5-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00202] Mp.: 246-247°C (ethyl acetate), yield: 64%.

Example 48

(±)-7-(2-Ethyl-3-oxo-2,3-dihydro-1,2,4-thiadiazol-5-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00203] Mp.: 250-256°C, yield: 60%.

Example 49

(±)-7-(4-Carboxythiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00204] A mixture of 9 ml of ethanol, 0.85 g (1.89 mmol) of (±)-7-(4-ethoxycarbonyl-thiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (Example 8) and 7 ml of 1N sodium hydroxide solution was stirred at 90°C. After cooling, it was acidified with acetic acid, diluted with water and the precipitated crystals were filtered off, washed with water and dried to yield 0.78 g (98%) of the title compound; Mp.: >260°C.

Example 50

(±)-8-Methyl-5-(4-nitrophenyl)-7-(5-tetrazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00205] A mixture of 0.60 g (1.70 mmol) of the starting material XXIII, 3 ml of dimethylformamide, 0.12 g (1.87 mmol) of sodium azide and 0.10 g (1.87 mmol) of ammonium chloride was stirred at 140°C for 30 min. The cooled reaction mixture was diluted with water and the precipitated crystals were filtered off. The so obtained product was purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of chloroform - methanol (99:1) as eluent to yield 0.68 g (54%) of the title compound; Mp.: 263-264°C.

Example 51

[00206] (±)-8-Methyl-5-(4-nitrophenyl)-7-(1,2,4-oxadiazol-3-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00207] A mixture of 1.50 g (3.91 mmol) of the starting material XXIV and 15 ml of triethyl orthoformate in the presence of 0.05 ml of 36% hydrochloric acid was stirred at 110°C for 30 min, then concentrated in vacuum. The residue was stirred with water, the precipitated crystals were filtered off, washed with water and recrystallized from 2-methoxyethanol to yield 1.15 g (75%) of the title compound; Mp.: 190-196°C.

Example 52

(±)-8-Methyl-7-(5-methyl-1,2,4-oxadiazol-3-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00208] A mixture of 3.0 g (7.82 mmol) of the starting material XXIV and 15 ml of acetic anhydride was stirred at 110°C for 1 h, then after cooling it was diluted with water and extracted with dichloromethane. The organic layer was concentrated and the residue was purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of n-hexane – ethyl acetate (2:1) as eluent to yield 1.58 g (50%) of the title compound; Mp.: 191-200°C.

Example 53

(±)-8-Methyl-7-(2-methylthiazol-4-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(±)-7-Bromoacetyl-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00209] A mixture of 4.80 g (14.7 mmol) of the starting material I, 24 ml of dimethylformamide, 2.16 g (15.5 mmol) of bromoacetic acid and 4.56 g (22 mmol) of dicyclohexylcarbodiimide was stirred for 20 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was taken up in ethyl acetate, washed with water, concentrated and recrystallized from ethanol to yield 4.83 g (73%) of the title compound; Mp.: 183-186°C.

Step B

[00210] The product obtained in Step A was dissolved in 45 ml of dimethylformamide and after adding 4.96 g (65 mmol) of thioacetamide it was stirred at 80°C for 1 h, then cooled and poured into water. The precipitated crude product was filtered off, washed with water and purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of hexane – ethyl acetate (9:1) as eluent to yield 1.67 g (37%) of the title compound; Mp.: 178-190°C.

Example 54

(±)-8-Methyl-5-(4-nitrophenyl)-7-(2-pyrimidinyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

1-{6-[(4-Nitrophenyl)-(pyrimidin-2-yl-hydrazono)-methyl]-benzo-1,3-dioxol-5-yl}-propan-2-ol

[00211] A stirred mixture of 3.29 g (9.99 mmol) of (±)-7-methyl-5-(4-nitrophenyl)-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochroman-5-ol, 40 ml of ethyl acetate and 1.0 ml (1.15 mmol) of perchloric acid was refluxed for 1 h. After cooling the precipitated (±)-7-methyl-5-(4-nitrophenyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isochromen-6-ylium perchlorate was filtered off, and it was stirred at reflux temperature with 1.6 g (14.55 mmol) of 2-hydrazinopyrimidine in 50 ml of isopropanol for 2 h, then concentrated. The residue was dissolved in dichloromethane and washed several times with water. After drying and evaporation the crude product was purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of toluene – ethyl acetate (0.1:4) as eluent to yield 2.71 g (64%) of the title compound; Mp.: 125-127°C.

Step B

1-{6-[(4-Nitrophenyl)-(pyrimidin-2-yl-hydrazono)-methyl]-benzo-1,3-dioxol-5-yl}-propan-2-ol mesylate

[00212] 2.35 g (5.58 mmol) of the compound prepared in Step A was dissolved in 50 ml of dry dichloromethane. The solution was cooled to 0 °C and after addition of 2.1 ml (15.07 mmol) of triethylamine 0.87 ml (11.22 mmol) of methanesulfonyl chloride was added over a period of 20 min, then the mixture was stirred at room temperature for 3 h. After washing with water it was dried and concentrated to yield 2.69 g (54%) of the title compound as an intermediate; Mp.: 122-124°C.

Step C

[00213] A mixture of 3.13 g (6.27 mmol) of the compound obtained in Step B, 60 ml of a 1:1 mixture of dichloromethane - methanol and 0.52 ml (6.90 mmol) of 50% sodium hydroxide solution was stirred at room for 1.5 h. After filtration the reaction mixture was concentrated, the

residue was treated with water and recrystallized from three fold dimethylformamide containing 10 % water to yield 1.96 g (77%) of the title compound; Mp.: 261-263°C.

Example 55

(±)-7-(3-Chloropyridazin-6-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

1-{6-[(6-Chloropyridazin-3-yl)-hydrazono-(4-nitrophenyl)-methyl]-(benzo-1,3-dioxol-5-yl)}-propan-2-ol

[00214] A stirred mixture of 2.00 g (6.07 mmol) of (±)-7-methyl-5-(4-nitrophenyl)-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isochroman-5-ol, 32 ml of isopropanol, 0.3 ml of hydrochloric acid and 1.04 g (7.28 mmol) of 4-hydrazino-6-chloropyridazine was refluxed for 3 h. After diluting with water, the precipitated crystals were filtered off, dried and recrystallized first from ethyl acetate, then from dimethylformamide containing 10% water to yield 1.53 g (55%) of the title compound; Mp.: 135-137°C.

Step B

[00215] A mixture of 0.3 g (0.66 mmol) of the compound prepared in Step A, 10 ml of dimethylformamide and 0.34 g (1.30 mmol) of triphenylphosphine was stirred at room temperature for 5 min, then 0.20 ml (1.27 mmol) of diethyl azodicarboxylate was added and stirring was continued for 24 h. After dilution with sodium chloride solution the precipitated product was filtered off, dried and purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of chloroform - methanol (99:1) as eluent. The residue obtained on concentration was crystallized by refluxing in ethanol to yield 0.12 g (42%) of the title compound; Mp.: 254-255°C.

Example 56

(±)-8-Methyl-5-(4-nitrophenyl)-7-(1H(2H)-1,2,4-triazol-3-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(±)-8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-S-methyl-thiocarboximidate

[00216] The title compound was obtained from the starting material I in dimethylformamide with methyl iodide in the presence of potassium carbonate at room temperature. Mp.: 191-192°C, yield: 94%.

Step B

[00217] A mixture of 3.0 g (7.53 mmol) of the compound obtained in Step A, 110 ml of 2-methoxyethanol and 4.50 g (74.93 mmol) of formic hydrazide was stirred at 110°C in the presence of catalytic amount of p-toluenesulfonic acid for 16 h. The residue obtained on concentration was treated with 10 % sodium carbonate solution, the obtained crude product was filtered, dried and purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of hexane – ethyl acetate (1:2) as eluent to yield 1.86 g (63%) of the title compound; Mp.: 154-156°C.

Example 57

(±)-8-Methyl-7-(5-methyl-2(1)H-1,2,4-triazol-3-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00218] A mixture of 15 ml of 2-methoxyethanol, 0.41 g (1.03 mmol) of (±)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-S-methyl-thiocarboximidate (Step A of Example 56) and 0.35 g (4.68 mmol) of acetic hydrazide was stirred at 110°C in the presence of catalytic amount of p-toluenesulfonic acid for 16 h. The residue obtained on concentration was treated with 10% sodium carbonate solution, the obtained crude product was filtered, dried and purified by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and a mixture of hexane – ethyl acetate (1:2) as eluent to yield 0.32 g (78%) of the title compound; Mp.: 144-147°C (solid foam).

Example 58

(±)-7-(1,5-Dimethyl-1H-1,2,4-triazol-3-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (isomer I) and (±)-7-(2,5-dimethyl-2H-1,2,4-triazol-3-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (isomer II)

[00219] A mixture of 0.57 g (5.08 mmol) of potassium tert-butoxide, 2.05 g (5.04 mmol) of (±)-8-methyl-7-(5-methyl-2(1)H-1,2,4-triazol-3-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (Example 57), 40 ml of tetrahydrofuran and 0.32 ml (5.14

mmol) of methyl iodide was stirred at room temperature for 16 h. then the reaction mixture was diluted with water, extracted with ethyl acetate, the organic layer was dried and concentrated. The two products formed in the reaction were separated by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and ethyl acetate as eluent. Isomer *II*, having R_F: 0.55 was first obtained, which was refluxed in ethanol to yield 0.30 g (14 %), Mp.: 185-187 °C. Then isomer *I* was collected, having R_F: 0.26, which after refluxing in ethanol weighed 0.67 g (32%), Mp.: 193-195°C.

Example 59

(±)-8-Methyl-7-(1-methyl-1H-1,2,4-triazol-3-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (isomer I) and (±)-8-methyl-7-(2-methyl-2H-1,2,4-triazol-3-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (isomer II)

[00220] A mixture of 0.41 g (3.65 mmol) of potassium tert-butoxide, 1.4 g (3.57 mmol) of (±)-8-methyl-5-(4-nitrophenyl)-7-(1H(2H)-1,2,4-triazol-3-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (Example 56), 35 ml of tetrahydrofuran and 0.23 ml (3.69 mmol) of methyl iodide was stirred at room temperature for 16 h. After dilution with water the reaction mixture was extracted with ethyl acetate, the organic layer was dried and concentrated. The two products formed in the reaction were separated by column chromatography using silica gel (MN Kieselgel 60) as adsorbent and ethyl acetate as eluent. Isomer *I*, having R_F: 0.22, weighed 0.37 g, yield: 26%, Mp.: 115-117°C. Isomer *II*, having R_F: 0.63, was 0.35 g, yield: 24 %, Mp.: 92-94°C.

Examples 60-119

General procedures for reduction of the nitro groups of the compounds obtained in the above examples

Method A

[00221] 2.0 mmol of nitro compound was dissolved in a mixture of methanol - dichloromethane and after adding 6-10 mmol of 85-98% hydrazine hydrate and 0.1-2 g RaNi catalyst the mixture was stirred at 20-40°C for 1-5 h. After filtration of the catalyst the filtrate was concentrated, the residue was treated with water and the product was filtered off.

Method B

[00222] 5.5 g of RaNi catalyst was prehydrogenated in 250 ml of a 2:1 mixture of methanol - dichloromethane, then 20.0 mmol of nitro compound was added in 250 ml of the above solvent mixture and the so obtained mixture was hydrogenated at atmospheric pressure. After filtration of the catalyst the filtrate was concentrated, the residue was treated with water, the product was filtered, washed and dried.

Method C

[00223] A stirred mixture of 1.82 mmol of nitro compound, 30 ml of ethanol and 2.46 g (10.91 mmol) of tin (II) chloride dihydrate was refluxed for 3 h. The reaction mixture was concentrated, then aqueous sodium hydrogen carbonate and ethyl acetate were added to the residue. After separation the water phase was extracted with ethyl acetate, the combined organic layers were washed with sodium chloride solution, dried and concentrated. If necessary the residue was purified either by column chromatography or by recrystallization.

Method D

[00224] 3.4 mmol of nitro compound was dissolved in 35 ml of a mixture of methanol - dichloromethane (1:1), 0.4 g of a 10% palladium on activated carbon catalyst and 0.47 g of potassium carbonate were added and the so obtained mixture was hydrogenated in the presence of 1 ml of water. After completion of the reaction the catalyst was filtered off, the filtrate was concentrated, the residue was treated with water and filtered.

Method E

[00225] 4.0 mmol of nitro compound was dissolved in 48 ml of methanol containing 5% water, then after addition of 0.20 g of the catalyst 10% palladium on activated carbon 3.5 equivalent of a concentrated aqueous solution of potassium formate was added dropwise at room temperature and the mixture was stirred at the above temperature. After completion of the reaction the catalyst was filtered off, the filtrate was concentrated, the residue is treated with water and filtered.

Table 10.
2,3-Benzodiazepines containing aminophenyl group
(The ^{1}H NMR spectra were recorded at 250 MHz unless stated otherwise)

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
60	(±)-5-(4-Aminophenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	187-190	78
Method A	^{1}H NMR ($CDCl_3$) δ 1.32 (3H, d, 6.5 Hz), 2.78 (1H, dd, 14.0 Hz, 9.7 Hz), 2.97 (1H, dd, 14.0 Hz, 4.9 Hz), 3.80 (2H, br), 5.26 (1H, m), 5.98 (2H, m), 6.65 (1H, s), 6.67 (1H, d, 4.0 Hz), 6.73 (2H, dm), 6.80 (1H, s), 7.37 (1H, d, 4.0 Hz), 7.55 (2H, dm) MS: EI(70eV): $[M]^{+\cdot}$: 378, *m/z:* 363, 279, 278, 253, 252		
61	(R)-5-(4-Aminophenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	125-130	84 -578° (c=1, $CHCl_3$)
Method A	^{1}H NMR ($CDCl_3$) δ 1.29 (3H, d, 6.5 Hz), 2.77 (1H, dd, 14.0 Hz, 9.7 Hz), 3.00 (1H, dd, 14.0 Hz, 4.9 Hz), 3.92 (2H, br), 5.23 (1H, m), 5.98 (2H, m), 6.62 (1H, d, 4.0 Hz), 6.65 (1H, s), 6.72 (2H, dm), 6.80 (1H, s), 7.32 (1H, d, 4.0 Hz), 7.55 (2H, dm)		
62	(S)-5-(4-Aminophenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	124-128	94 +546° (c=0.34, $CHCl_3$)
Method A	^{1}H NMR (DMSO-d_6) δ 1.15 (3H, d, 6.5 Hz), 2.60 (1H, dd, 13.6 Hz, 10.5 Hz), 2.94 (1H, dd, 13.6 Hz, 4.8 Hz), 4.99 (1H, m), 5.72 (2H, br), 6.03 (2H, m), 6.60 (2H, dm), 6.62 (1H, s), 6.81 (1H, d, 4.0 Hz), 7.04 (1H, s), 7.27 (1H, d, 4.0 Hz), 7.55 (2H, dm) MS: EI(70eV): $[M]^{+\cdot}$: 378, *m/z:* 377, 363, 279, 278, 253, 252 CI: $[M+H]^+$: 379, $[M]^{+\cdot}$:378, *m/z*: 363		
63	(±)-5-(4-Aminophenyl)-8-methyl-7-(4-methyl-thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	190-191 (EtOH)	65
Method A	^{1}H NMR ($CDCl_3$) δ 1.30 (3H, d, 6.5 Hz), 2.29 (3H, s), 2.77 (1H, dd, 14.0 Hz, 10.0 Hz), 2.92 (1H, dd, 14.0 Hz, 5.1 Hz), 3.94 (2H, br), 5.27 (1H, m), 5.97 (2H, m), 6.20 (1H, s), 6.53 (2H, dm), 6.70 (1H, s), 6.88 (1H, s), 7.53 (2H, dm)		
64	(±)-5-(4-Aminophenyl)-8-methyl-7-(5-methyl-thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	165-167	47
Method A	^{1}H NMR (DMSO-d_6) δ 1.17 (3H, d, 6.5 Hz), 2.25 (3H, s), 2.60 (1H, dd, 13.9 Hz, 10.3 Hz), 2.94 (1H, dd, 13.9 Hz, 5.1 Hz), 4.95 (1H, m), 5.70 (2H, br), 6.05 (2H, dm), 6.57 (1H, s), 6.62 (2H, dm), 6.93 (1H, s), 7.04 (1H, s), 7.36 (2H, dm)		
65	(±)-5-(4-Aminophenyl)-8-methyl-7-(4,5-dimethyl-thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	240-242 (EtOH)	83
Method A	^{1}H NMR (DMSO-d_6) δ 1.16 (3H, d, 6.5 Hz), 2.06 (3H, s), 2.13 (3H, s), 2.62 (1H, dd, 14.0 Hz, 10.0 Hz), 2.92 (1H, dd, 14.0 Hz, 5.0 Hz), 4.97 (1H, m), 5.70 (2H, br), 6.04 (2H, dm), 6.60 (1H, s), 6.62 (2H, dm), 7.02 (1H, s), 7.34 (2H, dm)		
66	(±)-5-(4-Aminophenyl)-7-(4-phenyl-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	221-223 (EtOH)	89

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
Method A	^{1}H NMR ($CDCl_3$) δ 1.29 (3H, d, 6.5 Hz), 2.80 (1H, dd, 14.0 Hz, 9.4 Hz), 3.00 (1H, dd, 14.0 Hz, 4.8 Hz), 3.93 (2H, br), 5.40 (1H, m), 5.98 (2H, m), 6.62 (1H, s), 6.70 (2H, dm), 6.78 (1H, s), 7.29 (1H, t), 7.39 (1H, t), 7.50 (1H, s), 7.57 (2H, dm), 7.86 (2H, d)		
67	(±)-5-(4-Aminophenyl)-7-(4-ethoxycarbonyl-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	251-252 (EtOH)	83
Method A	^{1}H NMR ($CDCl_3$) δ 1.29 (3H, d, 6.5 Hz), 1.38 (3H, t), 2.76 (1H, dd, 14.0 Hz, 10.0 Hz), 2.92 (1H, dd, 14.0 Hz, 5.0 Hz), 3.98 (2H, br), 4.33 (2H, q), 5.40 (1H, m), 6.00 (2H, m), 6.68 (1H, s), 6.69 (2H, dm), 6.82 (1H, s), 6.86 (1H, s), 7.51 (2H, dm)		
68	(±)-5-(4-Aminophenyl)-7-(4,5-dihydro-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	145-150 (EtOH)	84
Method A	^{1}H NMR ($CDCl_3$) δ 1.21 (3H, d, 6.5 Hz), 2.70 (1H, dd, 14.0 Hz, 10.0 Hz), 2.96 (1H, dd, 14.0 Hz, 5.0 Hz), 3.20 (1H, m), 3.70 (1H, m), 3.90 (2H, br), 4.17 (2H, m), 5.09 (1H, m), 5.98 (2H, dm), 6.60 (1H, s), 6.66 (2H, dm), 6.73 (1H, s), 7.47 (2H, dm) MS: EI(70eV): $[M]^{+\cdot}$: 380, *m/z:* 365, 339, 279, 264, 253, 252		
69	(R)-5-(4-Aminophenyl)-7-(4,5-dihydro-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	148-150 (EtOH)	82 -239° (c=0.5, $CHCl_3$)
Method A	^{1}H NMR (DMSO-d_6) δ 1.16 (3H, d, 6.5 Hz), 2.60 (1H, dd, 14.0 Hz, 10.0 Hz), 2.90 (1H, dd, 14.0 Hz, 4.0 Hz), 3.25 (2H, m), 4.00 (2H, m), 4.82 (1H, m), 5.73 (2H, br), 6.07 (2H, dm), 6.64 (s), 6.64 (2H, dm), 7.02 (1H, s), 7.30 (2H, dm) MS: EI(70eV): $[M]^{+\cdot}$: 380, *m/z:* 365, 339, 279, 278, 264, 253, 252 CI: $[M+H]^+$: 381, $[M]^{+\cdot}$: 380, *m/z*: 279		
70	(S)-5-(4-Aminophenyl)-7-(4,5-dihydro-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	150-152	92 +175° (c=0.51, $CHCl_3$)
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 380, *m/z:* 365, 339, 279, 278, 264, 253, 252 CI: $[M+H]^+$: 381, $[M]^{+\cdot}$: 380, *m/z*: 279		
71	(±)-5-(4-Aminophenyl)-7-(4,5-dihydro-4-oxo-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	218-220 (EtOH)	85
Method A	^{1}H NMR (DMSO-d_6) δ 1.29 (3H, d, 6.5 Hz), 2.61 (1H, dd, 13.0 Hz, 12.0 Hz), 2.96 (1H, dd, 13.0 Hz, 5.0 Hz), 3.72 (2H, m), 5.08 (1H, m), 6.01 (2H, br), 6.06 (2H, dm), 6.60 (2H, dm), 6.62 (1H, s), 7.10 (1H, s), 7.40 (2H, dm)		
72	(±)-5-(4-Aminophenyl)-7-(4,5-dihydro-5-methyl-4-oxo-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	200-204 (EtOH)	63
Method A	^{1}H NMR (DMSO-d_6) δ 1.32 (d) and 1.45 (d, overlapping, diastereomers), 2.60 (1H, dd, 13.0 Hz, 12.0 Hz), 2.94 (1H, dd, 13.0 Hz, 5.0 Hz), 3.96 and 4.05 (1H, q), 5.08 (1H, m), 6.0 (2H, br), 6.07 (2H, dm), 6.60 (2H, dm), 6.62 (1H, s), 7.08 (1H, s), 7.40 (2H, dm) MS: EI(70eV): $[M]^{+\cdot}$: 408, *m/z:* 393, 279, 265, 253, 252		

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
73	(±)-5-(4-Aminophenyl)-7-(5,6-dihydro-4-oxo-4H-1,3-thiazin-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	226-228 (EtOH)	90
Method A	^{1}H NMR (DMSO-d_6) δ 1.25 (3H, d, 6.5 Hz), 2.35 (2H, m), 2.57 (1H, dd, 13.0 Hz, 12.0 Hz), 2.88 (1H, dd, 13.0 Hz, 4.0 Hz), 3.05 (2H, m), 5.21 (1H, m), 5.97 (2H, br), 6.09 (2H, dm), 6.60 (1H, s), 6.62 (2H, dm), 7.04 (1H, s), 7.42 (2H, dm) MS: EI(70eV): $[M]^{+\cdot}$: 408, *m/z*: 295, 279, 253, 252		
74	5-(4-Aminophenyl)-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	200-204	52
Method A	^{1}H NMR (DMSO-d_6) δ 2.88 (2H, t), 4.21 (2H, t), 5.70 (2H, s), 6.08 (2H, s), 6.60 (1H, s), 6.62 (2H, dm), 6.89 (1H, d, 4.0 Hz), 7.08 (1H, s), 7.28 (1H, d, 4.0 Hz), 7.37 (2H, dm)		
75	(±)-5-(4-Amino-3-methylphenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	225-227	78
Method B	MS: EI(70eV): $[M]^{+\cdot}$: 392, *m/z*: 377, 293, 266 CI: $[M+H]^+$: 393, $[M]^{+\cdot}$: 392, *m/z*: 266		
76	(±)-1-(4-Aminophenyl)-4-methyl-8-methoxy-3-(2-thiazolyl)-4,5-dihydro-3H-[2,3]benzodiazepine	105-107	57
Method D	MS: EI(70eV): $[M]^{+\cdot}$: 364, *m/z*: 349, 265, 223 CI: $[M+H]^+$: 365, $[M]^{+\cdot}$: 364		
77	(±)-1-(4-Aminophenyl)-8-chloro-4-methyl-3-(2-thiazolyl)-4,5-dihydro-3H-[2,3]benzodiazepine	104-107	72
Method A	^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, 6.5 Hz), 2.96 (1H, dd, 13.0 Hz, 10.0 Hz), 3.10 (1H, dd, 13.0 Hz, 5.0 Hz), 5.35 (1H, m), 6.68 (1H, d, 4.0 Hz), 6.72 (2H, dm), 7.21 (1H, d, 4.0 Hz), 7.25 (1H, d, 1.0 Hz), 7.27 (1H, d, 7.0 Hz), 7.34 (1H, dd), 7.53 (2H, dm)		
78	(±)-1-(4-Aminophenyl)-8-chloro-4-methyl-3-(4-methyl-thiazol-2-yl)-4,5-dihydro-3H-[2,3]benzodiazepine	173-175	90
Method A	^{1}H NMR ($CDCl_3$) δ 1.26 (3H, d, 6.5 Hz), 2.27 (3H, d, 1.0 Hz), 2.81 (1H, dd, 14.0 Hz, 9.7 Hz), 3.02 (1H, dd, 14.0 Hz, 5.0 Hz), 3.95 (2H, br), 5.28 (1H, m), 6.20 (1H, q, 1.0 Hz), 6.70 (2H, dm), 7.17 (1H, d, 2.2 Hz), 7.22 (1H, d, 8.2 Hz), 7.33 (1H, dd, 8.2 Hz, 2.2 Hz), 7.51 (2H, dm)		
79	(±)-1-(4-Aminophenyl)-3-(4,5-dihydro-thiazol-2-yl)-8-chloro-4-methyl-4,5-dihydro-3H-[2,3]benzodiazepine	213-216 (MeOH)	79
Method A	^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d, 6.5 Hz), 2.68 (1H, dd, 14.0 Hz, 10.0 Hz), 3.06 (1H, dd, 14.0 Hz, 5.0 Hz), 3.20 (2H, m), 4.02 (2H, m), 5.68 (2H, s), 4.92 (1H, m), 6.60 (2H, dm), 7.09 (1H, d, 1.0 Hz), 7.28 (2H, dm), 7.41 (1H, d, 7.0 Hz), 7.48 (1H, dd)		
80	(±)-1-(4-Aminophenyl)-3-(4,5-dihydro-4-oxo-thiazol-2-yl)-8-chloro-4-methyl-4,5-dihydro-3H-[2,3]benzodiazepine	226-228 (iPrOH)	75

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
Method A	^{1}H NMR (DMSO-d_6) δ 1.32 (3H, d, 6.5 Hz), 2.68 (1H, dd, 13.8 Hz, 12.0 Hz), 3.08 (1H, dd, 13.8 Hz, 4.8 Hz), 3.77 (2H, m), 5.10 (1H, m), 6.12 (2H, br), 6.66 (2H, dm), 7.17 (1H, d, 2.0 Hz), 7.41 (2H, dm), 7.52 (1H, d, 8.0 Hz), 7.54 (1H, dd, 8.0 Hz, 2.0 Hz)		
81	(±)-1-(4-Aminophenyl)-7,8-dichloro-3-(4-methyl-thiazol-2-yl)-4-methyl-4,5-dihydro-3H-[2,3]benzodiazepine	182-184 (EtOH)	48
Method A	^{1}H NMR ($CDCl_3$) δ 1.28 (3H, d, 6.5 Hz), 2.30 (3H, s), 2.80 (1H, dd, 14.0 Hz, 9.6 Hz), 3.02 (1H, dd, 14.0 Hz, 4.9 Hz), 3.96 (2H, br), 5.31 (1H, m), 6.22 (1H, q, 1.0 Hz), 6.69 (2H, dm), 7.28 (1H, s), 7.39 (1H, s), 7.50 (2H, dm)		
82	(±)-5-(4-Aminophenyl)-7-(4,5-dihydro-oxazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	166-167 (EtOH)	87
Method A	^{1}H NMR (DMSO-d_6) δ 1.20 (3H, d, 6.5 Hz), 2.31 (1H, dd, 13.8 Hz, 12.0 Hz), 2.78 (1H, dd, 13.8 Hz, 5.8 Hz), 3.61 (2H, m), 4.18 (2H, m), 4.51 (1H, m), 5.66 (2H, br), 6.03 (2H, dm), 6.51 (1H, s), 6.53 (2H, dm), 6.98 (1H, s), 7.30 (2H, dm) MS: EI(70eV): $[M]^{+\cdot}$: 364, *m/z*: 349, 323, 279, 278, 252 CI: $[M+H]^+$: 365, $[M]^{+\cdot}$: 364		
83	(±)-5-(4-Aminophenyl)-8-methyl-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	192-194 (50 % EtOH-H_2O)	77
Method A	^{1}H NMR (DMSO-d_6) δ 1.20 (3H, d, 6.5 Hz), 2.62 (1H, dd, 13.9 Hz, 10.8 Hz), 2.99 (1H, dd, 13.9 Hz, 5.2 Hz), 5.01 (1H, m), 5.78 (2H, br), 6.03 (2H, dm), 6.58 (1H, s), 6.60 (2H, dm), 7.07 (1H, s), 7.32 (2H, dm,)		
84	(R)-5-(4-Aminophenyl)-8-methyl-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	219-220 (ethyl formate)	67 -490° (c=0.9, $CHCl_3$)
Method C	^{1}H NMR ($CDCl_3$) δ 1.33 (3H, d, 6.5 Hz), 2.80 (1H, dd, 14.0 Hz, 9.9 Hz), 2.97 (1H, dd, 14.0 Hz, 5.0 Hz), 4.02 (2H, br), 5.30 (1H, m), 5.98 (2H, dm), 6.65 (1H, s), 6.68 (2H, dm), 6.80 (1H, s), 7.51 (2H, dm,), 8.50 (1H, s)		
85	(±)-5-(4-Aminophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	143-148	89
Method A	^{1}H NMR ($CDCl_3$) δ 1.32 (3H, d, 6.5 Hz), 2.56 (3H, s), 2.76 (1H, dd, 14.0 Hz, 10.0 Hz), 2.93 (1H, dd, 14.0 Hz, 5.0 Hz), 4.00 (2H, br), 5.19 (1H, m), 5.98 (2H, dm), 6.64 (1H, s), 6.70 (2H, dm), 6.79 (1H, s), 7.48 (2H, dm,) MS: EI(70eV): $[M]^{+\cdot}$: 393, *m/z*: 378, 279, 278, 253, 252 CI: $[M+H]^+$: 394, $[M]^{+\cdot}$: 393, *m/z*: 252		
86	(R)-5-(4-Aminophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	168-170 (50 % EtOH-H_2O)	78 -482° (c=0.5, $CHCl_3$)
Method B, C	^{1}H NMR (DMSO-d_6) δ 1.23 (3H, d, 6.5 Hz), 2.50 (3H, s), 2.60 (1H, dd, 13.8 Hz, 9.6 Hz), 2.97 (1H, dd, 13.8 Hz, 4.9 Hz), 4.93 (1H, m), 5.78 (2H, br), 6.03 (2H, dm), 6.58 (1H, s), 6.60 (2H, dm), 7.09 (1H, s), 7.31 (2H, dm)		

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
87	(±)-5-(4-Aminophenyl)-7-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	145-148 (precipit. with water)	75
Method A	^{1}H NMR (DMSO-d_6) δ 0.88 (2H, m), 1.05 (2H, m), 1.22 (3H, d, 6.5 Hz), 2.22 (1H, m), 2.61 (1H, dd, 14.0 Hz, 10.0 Hz), 2.99 (1H, dd, 14.0 Hz, 5.0 Hz), 4.97 (1H, m), 5.78 (2H, br), 6.05 (2H, dm), 6.60 (1H, s), 6.63 (2H, dm), 7.06 (1H, s), 7.36 (2H, dm)		
88	(±)-5-(4-Aminophenyl)-7-(5-ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	135-138	67
Method A	^{1}H NMR ($CDCl_3$) δ 1.35 (3H, t), 1.36 (3H, d, 6.5 Hz), 2.79 (1H, dd, 14.0 Hz, 10.0 Hz), 2.98 (2H, q), 2.99 (1H, dd, 14.0 Hz, 5.0 Hz), 3.98 (2H, br), 5.25 (1H, m), 6.02 (2H, dm), 6.63 (1H, s), 6.73 (2H, dm), 6.82 (1H, s), 7.51 (2H, dm,)		
89	(R)-5-(4-Aminophenyl)-7-(5-ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	142-144 (precipit. with water)	47 -602° (c=0.5, EtOH)
Method E	MS: EI(70eV): $[M]^{+\cdot}$: 407, *m/z*: 392, 279, 278, 253, 252 CI: $[M+H]^+$: 408, $[M]^{+\cdot}$: 407		
90	(±)-5-(4-Aminophenyl)-8-methyl-7-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	216-218	33
Method A	^{1}H NMR ($CDCl_3$) δ 1.39 (3H, d, 6.5 Hz), 2.80 (1H, dd, 14.0 Hz, 10.0 Hz), 2.93 (1H, dd, 14.0 Hz, 5.0 Hz), 4.06 (2H, br), 5.28 (1H, dm), 6.00 (2H, dm), 6.61 (1H, s), 6.69 (2H, dm), 6.81 (1H, s), 7.48 (2H, dm,) MS: EI(70eV): $[M]^{+\cdot}$: 447, *m/z*: 432, 279, 253, 252 CI: $[M+H]^+$: 448, $[M]^{+\cdot}$: 447, *m/z*: 252		
91	(±)-5-(4-Aminophenyl)-7-(5-phenyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	228-230 (50 % EtOH-H_2O)	84
Method A	^{1}H NMR (DMSO-d_6) δ 1.28 (3H, d, 6.5 Hz), 2.67 (1H, dd, 14.0 Hz, 10.0 Hz), 3.01 (1H, dd, 14.0 Hz, 5.0 Hz), 5.02 (1H, m), 5.81 (2H, br), 6.07 (2H, dm), 6.59 (1H, s), 6.61 (2H, dm), 7.08 (1H, s), 7.40 (2H, dm), 7.45 (3H, m), 7.81 (2H, d) MS: EI(70eV): $[M]^{+\cdot}$: 455, *m/z*: 440, 295, 279, 253, 252 CI: $[M+H]^+$: 456, $[M]^{+\cdot}$: 455, *m/z*: 295		
92	(±)-5-(4-Aminophenyl)-7-(5-cyclopropylamino-methyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	135-138	35
Method A	^{1}H NMR ($CDCl_3$) δ 0.45 (4H, m), 1.33 (3H, d, 6.5 Hz), 2.28 (1H, m), 2.75 (1H, dd, 14.0 Hz, 9.9 Hz), 2.85 (1H, dd, 14.0 Hz, 4.9 Hz), 4.0 (2H, br), 4.10 (2H, s), 5.26 (1H, m), 6.00 (2H, m), 6.60 (1H, s), 6.68 (2H, dm), 6.80 (1H, s), 7.49 (2H, dm)		
93	(±)-1-(4-Aminophenyl)-8-chloro-4-methyl-3-(1,3,4-thiadiazol-2-yl)-4,5-dihydro-3H-[2,3]benzodiazepine	125-128	79

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
Method A	^{1}H NMR (DMSO-d_6) δ 1.18 (3H, d, 6.5 Hz), 2.69 (1H, dd, 14.0 Hz, 10.8 Hz), 3.14 (1H, dd, 14.0 Hz, 5.1 Hz), 5.05 (1H, m), 5.83 (2H, s), 6.62 (2H, dm), 7.10 (1H, s), 7.33 (2H, dm), 7.51 (2H, m)		
94	(±)-1-(4-Aminophenyl)-8-chloro-4-methyl-3-(5-methyl-1,3,4-thiadiazol-2-yl)-4,5-dihydro-3H-[2,3]benzodiazepine	131-133	88
Method A	^{1}H NMR (DMSO-d_6) δ 1.18 (3H, d, 6.5 Hz), 2.70 (1H, dd, 14.0 Hz, 10.3 Hz), 3.11 (1H, dd, 14.0 Hz, 5.3 Hz), 2.50 (3H, s), 4.96 (1H, m), 5.80 (2H, s), 6.62 (2H, dm), 7.10 (1H, s), 7.32 (2H, dm), 7.51 (2H, m)		
95	(±)-5-(4-Amino-3-methylphenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	140-144	72
Method B	MS: EI(70eV): $[M]^{+\cdot}$: 407, *m/z*: 392, 293, 266 CI: $[M+H]^+$: 408, $[M]^{+\cdot}$: 407, *m/z*: 266		
96	(±)-5-(3-Amino-4-methylphenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	125	70
Method B	^{1}H NMR (500 MHz) (DMSO-d_6) δ 1.17 (3H, d, 6.5 Hz), 2.10 (3H, s), 2.51 (3H, s), 2.72 (1H, dd, 14.1 Hz, 9.1 Hz), 3.05 (1H, dd, 14.1 Hz, 4.5 Hz), 5.01 (2H, s), 5.03 (1H, m), 6.07 (2H, dm), 6.55 (1H, s), 6.70 (1H, dd), 6.83 (1H, d, 1.2 Hz), 7.00 (1H, d, 7.8 Hz), 7.06 (1H, s)		
97	(±)-5-(3-Aminophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	197-198 (iPrOH)	77
Method B, C	^{1}H NMR (500 MHz) (DMSO-d_6) δ 1.17 (3H, d, 6.5 Hz), 2.51 (3H, s), 2.77 (1H, dd, 14.2 Hz, 8.6 Hz), 3.08 (1H, dd, 14.2 Hz, 4.3 Hz), 5.06 (1H, m), 5.24 (2H, s), 6.07 (2H, dm), 6.54 (1H, s), 6.67 (1H, d), 6.71 (1H, d), 6.74 (1H, d), 7.06 (1H, s)		
98	(±)-1-(4-Aminophenyl)-4-methyl-3-(5-methyl-1,3,4-thiadiazol-2-yl)-8-methoxy-4,5-dihydro-3H-[2,3]benzodiazepine	180-184	84
Method D	MS: EI(70eV): $[M]^{+\cdot}$: 379, *m/z*: 364, 265, 238, 223 CI: $[M+H]^+$: 380, $[M]^{+\cdot}$: 379, *m/z*: 223		
99	(±)-5-(4-Aminophenyl)-8-methyl-7-(5-methyl-6H-1,3,4-thiadiazin-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	154-157	85
Method A	^{1}H NMR (DMSO-d_6) δ 1.20 (3H, d, 6.5 Hz), 2.10 (3H, s), 2.55 (1H, dd, 14.0 Hz, 11 Hz), 2.92 (1H, dm), 2.92 (1H, dd, 14.5 Hz), 3.28 (1H, d, 14.5 Hz), 5.10 (1H, m), 5.70 (2H, s), 6.02 (2H, dm), 6.55 (2H, dm), 7.01 (1H, s), 7.38 (2H, dm), 7.60 (1H, s)		
100	(±)-5-(4-Aminophenyl)-7-(5,6-dihydro-5-oxo-4H-1,3,4-thiadiazin-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	172-176	83

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
Method A	^{1}H NMR (DMSO-d_6) δ 1.16 (3H, d, 6.5 Hz), 2.49 (1H, dd, 14.0 Hz, 10.0 Hz), 2.87 (1H, dd, 14.0 Hz, 5.2 Hz), 3.31 (2H, s), 4.78 (1H, m), 5.68 (2H, s), 6.05 (2H, dm), 6.65 (1H, s), 6.66 (2H, dm), 7.00 (1H, s), 7.32 (2H, dm), 10.5 (1H, s)		
101	(±)-5-(4-Aminophenyl)-8-methyl-7-(5-oxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	263-264	47
Method C	^{1}H NMR (DMSO-d_6) δ 1.17 (3H, d, 6.5 Hz), 2.58 (1H, dd, 14.0 Hz, 10.4 Hz), 2.97 (1H, dd, 14.0 Hz, 5.4 Hz), 4.71 (1H, m), 5.65 (2H, s), 6.04 (2H, dm), 6.61 (2H, dm), 6.62 (1H, s), 7.01 (1H, s), 7.23 (2H, dm), 11.81 (1H, brs) MS: EI(70eV): $[M]^{+\cdot}$: 395, *m/z*: 394, 306, 252 CI: $[M+H]^+$: 396, $[M]^{+\cdot}$: 395, *m/z*: 280		
102	(R)-5-(4-Aminophenyl)-8-methyl-7-(5-methyl-1,3,4-oxadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	145-149	86 -663° (c=0.5, EtOH)
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 377, *m/z*: 252 CI: $[M+H]^+$: 378, $[M]^{+\cdot}$: 377, *m/z*: 252		
103	(±)-5-(4-Aminophenyl)-8-methyl-7-(2-methyl-3-oxo-2,3-dihydro-1,2,4-thiadiazol-5-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	213 (EtOH)	67
Method A	^{1}H NMR (DMSO-d_6) δ 1.23 (3H, d, 6.5 Hz), 2.70 (1H, dd, 13.8 Hz, 10.2 Hz), 3.03 (1H, dd, 13.8 Hz, 4.2 Hz), 3.06 (3H, s), 4.91 (1H, m), 5.90 (2H, s), 6.08 (2H, dm), 6.61 (1H, s), 6.61 (2H, dm), 7.06 (1H, s), 7.30 (2H, dm)		
104	(±)-5-(4-Aminophenyl)-7-(2-cyclopropyl-3-oxo-2,3-dihydro-1,2,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	265-267	82
Method A	^{1}H NMR (DMSO-d_6) δ 0.85 (4H, m), 1.22 (3H, d, 6.5 Hz), 2.75 (1H, dd, 14.0 Hz, 10.0 Hz), 2.75 (1H, m), 3.02 (1H, dd, 14.0 Hz, 4.7 Hz), 4.92 (1H, m), 5.90 (2H, s), 6.07 (2H, dm), 6.60 (1H, s), 6.63 (2H, dm), 7.04 (1H, s), 7.30 (2H, dm)		
105	(±)-5-(4-Aminophenyl)-7-(2-ethyl-3-oxo-2,3-dihydro-1,2,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	212-214	59
Method A	^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t), 1.27 (3H, d, 6.5 Hz), 2.80 (1H, dd, 14.0 Hz, 9.0 Hz), 3.01 (1H, dd, 14.0 Hz, 4.0 Hz), 3.72 (2H, q), 4.07 (2H, br), 5.13 (1H, m), 6.03 (2H, dm), 6.65 (1H, s), 6.67 (2H, dm), 6.80 (1H, s), 7.37 (2H, dm) MS: EI(70eV): $[M]^{+\cdot}$: 423, *m/z*: 408, 279, 252, 160 CI: $[M+H]^+$: 424, $[M]^{+\cdot}$: 423		
106	(±)-5-(4-Aminophenyl)-7-(4-carboxy-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	>260 (dec.)	97
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 422, *m/z*: 407, 279, 253		

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
107	(±)-5-(4-Aminophenyl)-8-methyl-7-(5-tetrazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	>360	68
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 363, *m/z*: 295, 294, 252 CI: $[M+H]^+$: 364, $[M]^{+\cdot}$: 363, *m/z*: 295		
108	(±)-5-(4-Aminophenyl)-8-methyl-7-(1,2,4-oxadiazol-3-yl)-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine hydrochloride	124-126	48
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 363, *m/z*: 348, 253, 252 CI: $[M+H]^+$: 364, $[M]^{+\cdot}$: 363, *m/z*: 252		
109	(±)-5-(4-Aminophenyl)-8-methyl-7-(5-methyl-1,2,4-oxadiazol-3-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	130-135	74
Method A	MS: EI(70eV) (of the hydrochloride salt): $[M]^{+\cdot}$: 377, *m/z*: 362, 278, 252 CI: $[M+H]^+$: 378, $[M]^{+\cdot}$: 377, *m/z*: 252		
110	(±)-5-(4-Aminophenyl)-8-methyl-7-(2-methyl-thiazol-4-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	132-135	22
Method C	MS: EI(70eV): $[M]^{+\cdot}$: 392, *m/z*: 377, 279, 253, 252 CI: $[M+H]^+$: 393, $[M]^{+\cdot}$: 392		
111	(±)-5-(4-Aminophenyl)-8-methyl-7-(2-pyrimidinyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	233-235 (EtOH)	96
Method A	^{1}H NMR (DMSO-d_6) δ 1.23 (3H, d, 6.5 Hz), 2.50 (1H, dd, 14.0 Hz, 10.0 Hz), 2.89 (14.0 Hz, 4.8 Hz), 5.18 (1H, m), 5.71 (2H, s), 6.03 (2H, dm), 6.58 (2H, dm), 6.60 (1H, s), 6.60 (1H, t, 4.8 Hz), 7.43 (1H, s), 7.30 (2H, dm), 8.33 (2H, d, 4.8 Hz)		
112	(±)-5-(4-Aminophenyl)-7-(3-chloropyridazin-6-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	164-166 (EtOH)	94
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 407/409, *m/z*: 392/394, 355, 279, 278, 253, 252 CI: $[M+H]^+$: 408/410, $[M]^{+\cdot}$: 407/409, *m/z*: 279		
113	(±)-5-(4-Aminophenyl)-8-methyl-7-(1H(2H)-1,2,4-triazol-3-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	178-181	64
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 362, *m/z*: 347, 279, 252		
114	(±)-5-(4-Aminophenyl)-8-methyl-7-(5-methyl-1H(2H)-1,2,4-triazol-3-yl)-8,9-dihydro-7H-1,3-dioxolo-	166-169	72

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
	[4,5-h][2,3]benzodiazepine		
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 376, *m/z*: 361, 279, 252		
115	(±)-5-(4-Aminophenyl)-8-methyl-7-(2-methyl-2H-1,2,4-triazol-3-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	182-183	83
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 376, *m/z*: 361, 279, 252		
116	(±)-5-(4-Aminophenyl)-8-methyl-7-(1-methyl-1H-1,2,4-triazol-3-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	165-168	83
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 376, *m/z*: 361, 253, 252		
117	(±)-5-(4-Aminophenyl)-8-methyl-7-(2,5-dimethyl-2H-1,2,4-triazol-3-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	185-187	78
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 390, *m/z*: 375, 279, 265, 252		
118	(±)-5-(4-Aminophenyl)-8-methyl-7-(1,5-dimethyl-1H-1,2,4-triazol-3-yl)-8,9-dihydro-7H-1,3-dioxol [4,5-h][2,3]benzodiazepine	197-200	85
Method C	MS: EI(70eV): $[M]^{+\cdot}$: 390, *m/z*: 375, 253, 252		
119	(R)-5-(4-amino-3-methylphenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	158-160	83 -515° (c=0.38, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) δ 1.18 (3H, d, 5.4 Hz), 2.07 (s, 3H), 2.47 (s, 3H), 2.57 (dd, 1H, 13.7 Hz, 10.3 Hz), 2.95 (dd, 1H, 13.7 Hz, 4.9 Hz), 4.92 (m, 1H), 5.2-5.8 (br, 2H), 6.01 (s, br, 1H), 6.06 (s, br, 1H), 6.55 (s, 1H), 6.64 (d, 1H, 8.2Hz), 7.04 (s, 1H), 7.17 (d, 1H, 8.2 Hz), 7.25 (s, br, 1H) MS: EI(70eV): $[M]^{+\cdot}$: 407, *m/z*: 392, 293, 278, 266 CI: $[M+H]^+$: 408, $[M]^{+\cdot}$: 407		

Examples 120-131

General procedure for the synthesis of 2,3-benzodiazepines containing acetylamino-phenyl group

[00226] 2,3-benzodiazepines containing an aminophenyl group were dissolved in dichloromethane and stirred at room temperature with an excess of acetic anhydride. After completion of the reaction the mixture was washed with sodium hydrogen carbonate solution and water, then dried and concentrated.

Table 11.
2,3-benzodiazepine derivatives substituted with acetylaminophenyl group

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
120	(±)-5-(4-Acetylaminophenyl)-8-methyl-7-(5-methyl-thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	176-179	65
121	(±)-5-(4-Acetylaminophenyl)-8-methyl-7-(4-methyl-thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	236-238 (50 % EtOH-H_2O)	65
122	(±)-5-(4-Acetylaminophenyl)-7-(4,5-dihydro-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	211-213 (EtOH)	96
123	(R)-5-(4-Acetylaminophenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	126(rearrangement) 172-174 (EtOH)	95 -140° (c=0.44, $CHCl_3$)
124	(S)-5-(4-Acetylaminophenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	124-128	95 +134° (c=0.48, $CHCl_3$)
125	(R)-5-(4-Acetylaminophenyl)-7-(4,5-dihydro-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	143-145	95 +108° (c=0.45, $CHCl_3$)
126	(S)-5-(4-Acetylaminophenyl)-7-(4,5-dihydro-thiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	148-154	91 -111° (c=048, $CHCl_3$)
127	(±)-5-(4-Acetylaminophenyl)-7-(4,5-dihydro-oxazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	124-128	44
128	(±)-5-(4-Acetylaminophenyl)-8-methyl-7-(2-pyrimidinyl)-8,9-dihydro-7H-1,3-dioxolo-	162-163 (EtOH)	96

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
	[4,5-h][2,3]benzodiazepine		
129	(±)-5-(4-Acetylaminophenyl)-7-(3-chloro-pyridazin-6-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	164-170	78
130	(R)-5-(4-Acetylaminophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	276-277 (MeOH)	73 -114° (c=0.5, $CHCl_3$)
131	(±)-5-(4-Acetylamino-3-methylphenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	258-262	63

Example 132

(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-(4,5-dihydro-thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

[00227] *(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine*

[00228] This compound was prepared from starting compound XXXI according to the process described for starting compound I. Mp.: 123-125°C. Yield: 70%.

Step B

[00229] The product of Step A was transformed into the title compound according to the procedure described in Example 9. Mp.: 130-135°C. Yield: 81%.

Example 133

(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-(thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00230] The title compound was obtained from the intermediate described under Step A of Example 132 according to a method described in Example 1. Mp.: 138-142°C. Yield: 55%.

Example 134

(R)-7-(5-Ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

[00231] *(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl chloride*

[00232] This compound was prepared from starting compound XXXI according to the method described for starting compound XI. Mp.: 193-196°C. Yield: 85%. $[\alpha]_D$: -500.0°(c=0.5; $CHCl_3$).

Step B

[00233] 2.50 g (6.0 mmol) of the compound obtained in Step A was reacted with 1.28 g (21.3 mmol) of propionyl hydrazide in 10 ml of dimethylformamide at 70°C for 2 h. The cooled reaction mixture was poured onto water and the resulting precipitate was collected by filtration. This wet substance was further reacted in 24 ml of ethanol with 0.5 ml conc. hydrochloric acid at boiling point for 1 h. Solvent was evaporated and the residue was dissolved in dichloromethane and extracted with sodium bicarbonate solution and water. Evaporation of the solvent gave the crude title product which was purified by column chromatography using a mixture of n-hexane-ethyl acetate (1:1) as eluent, giving 1.15 g (yield: 49%) of the product. Mp.: 129-130°C.

Example 135

(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-(5-propyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00234] The title compound was obtained according to the method described in Example 134 but using butyric hydrazide. Mp.: 143-145°C. Yield: 73%. $[\alpha]_D$: +343.3°(c=0.5; $CHCl_3$).

Example 136

(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

[00235] *(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothiohydrazide*

[00236] The Step A intermediate of Example 134 was transformed into the carbothiohydrazide according to a method described for starting material XVIII. Mp.: 109-115°C. Yield: 91%. $[\alpha]_D$: -276.5°(c=0.5; $CHCl_3$).

Step B

[00237] The compound of Step A was reacted with triethyl orthoformate and a catalytic amount of hydrochloric acid similarly to a method described in Example 25, to give the title product. Mp.: 182-189°C. Yield: 92%. $[\alpha]_D$: +356.0°(c=0.5; $CHCl_3$).

Example 137

(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-(5-methoxymethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00238] The compound of Step A of Example 136 (2.07 g, 5.0 mmol) was reacted in 10 ml of dimethylformamide with 1.86 g (5.5 mmol) of pentachlorophenol methoxyacetate at 50°C for 2 h. The reaction mixture was diluted with water and the resulting precipitate was isolated by filtration. This wet intermediate was taken up in ethanol (24 ml), 0.50 ml of conc. hydrochloric acid was added and it was boiled for 1 h. Evaporation of the solvent gave a residue, which was dissolved in methylene chloride and the solution was washed with a 5% sodium carbonate solution and water. Evaporation of the solvent resulted in the crude title product that was purified with column chromatography; a mixture of n-hexane-ethyl acetate (2:1) was used as eluent to give 2.21 g of the pure product. Mp.: 153-155°C. Yield: 91%. $[\alpha]_D$: +317.5°(c=0.5; $CHCl_3$).

[00239] The compounds of Examples 138-148 were prepared analogously to the method described in Example 137 using the appropriate activated carboxylic acid derivatives as reagents (e.g.: acyl chloride, acid anhydride, pentachlorophenol ester, N-hydroxysuccinimide ester of the corresponding carboxylic acids).

Example 138

(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-(5-isopropyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00240] Mp.: 130-133°C. Yield: 90%.

Example 139

(R)-7-(5-Cyclopropyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00241] Mp.: 126-130°C. Yield: 93%.

Example 140

(R)-7-(5-Hydroxymethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00242] Mp.: 142-145°C. Yield: 67%.

Example 141

(R)-7-(5-Acetoxymethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00243] Mp.: 110-115°C. Yield: 97%.

Example 142

(R)-7-(5-Cyanomethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00244] Mp.: 118-122°C. Yield: 98%.

Example 143

(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-(5-methylthiomethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00245] Mp.: 132-134°C. Yield: 96%.

Example 144

(R)-7-(5-Ethoxycarbonyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00246] Mp.: 115-118°C. Yield: 80%. $[\alpha]_D$: +140.3°(c=0.5; $CHCl_3$).

Example 145

(R)-7-(5-Benzyloxycarbonyl-aminomethyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00247] Mp.: 240-243°C. Yield: 95%.

Example 146

(R)-8-Methyl-5-(3-methyl-4-nitrophenyl)-7-{5-[1-(1E)-propen-1-yl]-1,3,4-thiadiazol-2-yl}-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00248] Mp.: 232-237°C. Yield: 28%. $[\alpha]_D$: -359.2°(c=0.4; $CHCl_3$).

Example 147

(R)-7-(5-Hexyl-1,3,4-thiadiazol-2-yl)-8-methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00249] Mp.: 217-224°C. Yield: 66%.

Example 148

(R)-7-(5,6-Dihydro-5-oxo-4H-1,3,4-thiadiazin-2-yl)-8-methyl-5-(3-methyl-4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00250] The title compound was prepared from the compound obtained in Step A of Example 136 applying the method described in Example 43, however pentachlorophenol chloroacetate was used as alkylating agent. Mp.: 207-211°C. Yield: 70%. $[\alpha]_D$: +378.5°(c=0.5; $CHCl_3$).

Example 149

(R)-8-Methyl-5-(4-nitrophenyl)-7-(1,3,4-oxadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00251] The title compound was obtained from (R)-N'-{8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl}-formic hydrazide, according to the method described in Example 45. Mp.: 145-147°C. Yield: 35%, $[\alpha]_D$: -604.0°(c=0.5; $CHCl_3$).

Example 150

(±)-8-Methyl-5-(4-nitrophenyl)-7-(1,2,3,4-thiatriazol-5-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00252] A solution of 1.00 g (2.5 mmol) of starting material XVIII, 0.37 ml (4.6 mmol) of trifluoroacetic acid in 10 ml of formamid was stirred at 25°C for 5 min. Then a solution of 0.16 g (2.5 mmol) of sodium nitrite in 0.30 ml of water was added dropwise. After 0.5 h the reaction mixture was diluted with water and the precipitate formed was filtered off, washed with water and dried to yield 0.92 g (90%) of the title compound. Mp.: 109-110°C.

Example 151

(±)-8-Methyl-5-(4-nitrophenyl)-7-(2-methyl-1,3-oxazol-5-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

[00253] *(±)-N'-{2-[8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepin-7-yl]-2-oxoethyl}-acetamide*

[00254] A solution of 1.5 g (4.6 mmol) of (±)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine, 0.5 g (4.6 mmol) of N-acetylglycine and 1.0 g (5.0 mmol) of 1,3-dicyclohexylcarbodiimid was stirred in 15 ml of dichloromethane at 25°C for 3 h. The precipitated 1,3-dicyclohexylurea was filtered off and the filtrate was evaporated to dryness. The

crude product was purified by column chromatography using a mixture of ethyl acetate-hexane (1:1) as eluent to yield 1.1 g (58%) of the title compound.

Step B

[00255] 0.74 g (2.8 mmol) of triphenylphosphine was dissolved in 10 ml of dichloromethane and a solution of 0.2 ml (2.8 mmol) of bromine in 1 ml of dichloromethane was added. After 30 min a solution of 1.0 g (2.4 mmol) of the compound prepared in Step A and 1.0 ml (7.1 mmol) of triethylamine in 5 ml of dichloromethane was added and the mixture was boiled under nitrogen for 3 h. The resulting solution was washed with water, dried and concentrated to dryness. The crude product was purified by column chromatography using a mixture of ethyl acetate-hexane (1:1) as eluent to yield 0.6 g (62%) of the title compound. Mp.: 203-205°C.

Example 152

(±)-7-(2,4-dimethyl-1,3-oxazol-5-yl)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00256] The title compound was obtained according to the method described in Example 151, but using (±)-N-{2-[8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-yl]-1-methyl-2-oxoethyl}-acetamide as intermediate. Mp.: 76-78°C; yield: 68%.

Example 153

(R)-5-(3-Chloro-4-nitrophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00257] Step A

[00258] *(R)-7-(tert-Butoxycarbonyl)-5-(3-chloro-4-nitrophenyl)-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine*

[00259] The compound was prepared according to a synthesis described in literature (Anderson *et al., J. Am Chem Soc.* 117: 12358 (1995)) using 3-chloro-4-nitrobenzaldehyde and tert-butyl carbazate as key reagents. Mp.: 160-162°C.

Step B

(R)-5-(3-Chloro-4-nitrophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00260] The compound obtained in Step A (8.2 g; 18.2 mmol) was dissolved in ethyl acetate, containing 12% hydrochloric acid (82 ml). The solution was maintained at RT for 3 h. Then the solvent was evaporated and the residue was dissolved in ethyl acetate and washed with saturated sodium hydrogencarbonate solution and water. Evaporation yielded 5.3 g (81%) of the title product. Mp.: 165-170°C. $[\alpha]_D$: +65.0°(c=0.5; $CHCl_3$).

Step C

(R)-5-(3-Chloro-4-nitrophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl chloride

[00261] The compound was prepared from the intermediate obtained in Step B according to the method described for starting material XI. Mp.: 132-134°C. Yield: 88%. $[\alpha]_D$: -533.0°(c=0.5; $CHCl_3$).

Step D

[00262] The title compound was obtained from the compound prepared in Step C according to a method described in Method B of Example 28. Mp.: 151-152°C. Yield: 89%. $[\alpha]_D$: +284.1°(c=0.5; $CHCl_3$).

Example 154

(R)-5-(3-Chloro-4-nitrophenyl)-8-methyl-7-(5-methoxymethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(R)-5-(3-Chloro-4-nitrophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothiohydrazide

[00263] The compound obtained in Step C of Example 153 was transformed into the title compound according to a method described for starting material XVIII. Mp.: 126-127°C; yield: 85%.

Step B

[00264] The compound obtained in Step A was used to prepare the title compound according to the method described in Example 137. Mp.: 208-210°C; yield: 65%. $[\alpha]_D$: +470.6°(c=0.5; $CHCl_3$).

Example 155

(±)-8-Methyl-7-(3-methyl-isoxazol-5-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(±)-1-{8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepin-7-yl}-butane-1,3-dione

[00265] A solution of 4.0 g (12.3 mmol) of (±)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine, 0.52 ml (13.5 mmol) of diketene in 80 ml of toluene was stirred at 80°C for 3 h. The reaction mixture was washed with water, dried and concentrated. The residue was triturated with diisopropyl ether to yield 4.0 g (80%) of the title compound. Mp.: 169-171°C.

Step B

(±)-4-{8-Methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepin-7-yl}-4-thioxo-butan-2-one

[00266] A solution of 3.0 g (7.2 mmol) of a compound of Step A 2.4 g (5 mmol) of Lawesson's reagent in 500 ml of toluene was stirred at reflux temperature for 4 h. Then the reaction mixture was filtered and the solvent evaporated. The crude product was purified by column chromatography using a mixture of ethyl acetate-hexane (1:3) as eluent to yield 2.1 g (70%) of the title compound. Mp.: 178-185°C.

Step C

[00267] A solution of 1.9 g (4.5 mmol) of the compound obtained in Step B and 0.6 g (9.0 mmol) hydroxylamine hydrochloride was stirred in 20 ml of ethanol and heated at reflux for

3 h. The reaction mixture was diluted with water and the precipitate formed was filtered off. The crude product was purified by column chromatography using a mixture of ethyl acetate-hexane (1:3) as eluent to yield 0.60 g (32%) of the title compound. Mp.: 179-182°C.

Example 156

(R)-5-(3,5-Dimethyl-4-nitrophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(R)-7-(tert-Butoxycarbonyl)-5-(3,5-dimethyl-4-nitrophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00268] The compound was prepared according to a synthesis described in literature (Anderson *et al., J. Am. Chem. Soc.* 117: 12358 (1995)), however as key reagents 3,5-dimethyl-4-nitrobenzaldehyde and tert-butyl carbazate were used. Mp.: 222-223°C. $[\alpha]_D$: -443.0° (c=0.5; $CHCl_3$).

Step B

(R)-5-(3,5-Dimethyl-4-nitrophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00269] The compound obtained in Step A was subjected to hydrolysis according to a method described in Example 153 under Step B. Mp.: 193°C; yield: 88%. $[\alpha]_D$: +181° (c=0.5; $CHCl_3$).

Step C

(R)-5-(3,5-Dimethyl-4-nitrophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl chloride

[00270] The compound obtained in Step B was transformed into the title carbothioyl derivative according to a method described for starting compound XI. Mp.: 216°C; yield: 82%. $[\alpha]_D$: -389° (c=0.5; $CHCl_3$).

Step D

[00271] The title compound of this example was prepared from compound obtained in Step C according to Method B described in Example 28. Mp.: 235°C; yield: 86%. $[\alpha]_D$: +221° (c=0.5; $CHCl_3$).

Example 157

(R)-5-(3,5-Dimethyl-4-nitrophenyl)-8-methyl-7-(5-methyl-1,3,4-oxadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00272] The thiosemicarbazide type intermediate of Step D of Example 156 was treated with mercury(II)acetate for 16 h according to a procedure described in Example 45. Mp.: 132-133°C; yield: 90%. $[\alpha]_D$: -436° (c=0.5; $CHCl_3$).

Example 158

(R)-5-(3,5-Dimethyl-4-nitrophenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(R)-5-(3,5-Dimethyl-4-nitrophenyl)-8-methyl-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00273] This intermediate was prepared from the compound obtained in Step B of Example 156 by a method described for starting material I, however, during the reaction significant hydrolysis of the title product to the corresponding urea derivative was noticed as well. Title compound was isolated by column chromatography using a mixture of hexane-ethyl acetate (3:1) as eluent. Mp.: 228-230°C; yield: 18%.

Step B

[00274] Intermediate compound obtained in Step A was reacted with bromoacetaldehyde diethyl acetal as described in Example 1. Mp.: 167°C; yield: 46%.

Example 159

(R)-8-Methyl-7-(2-methyl-3-oxo-2,3-dihydro-1,2,4-thiadiazol-5-yl)-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(R)-Phenyl-(8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-3-carbothioyl)-carbamate

[00275] Prepared according to the procedure described for starting compound XXVI, however, from (R)-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine. The crude product was used without further purification.

Step B

(R)-1-Methyl-3-{8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl}-urea

[00276] Intermediate of Step A was reacted with methylamine according to the method described for the racemic starting compound XXVII. Mp.: 164°C; yield: 63%.. $[\alpha]_D$: -526° (c=0.5; $CHCl_3$).

Step C

[00277] The compound of Step B was reacted with bromine according to a procedure described in Example 46 to give the title product. Mp.: 177-180°C; yield: 98%. $[\alpha]_D$: +438° (c=0.5; $CHCl_3$).

Example 160

(±)-7-(5,5-Dimethyl-4-oxo-4,5-dihydro-thiazol-2-yl)-8-methyl-5-(4-nitrophenyl)-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00278] To a suspension of 1.20 g (2.86 mmol) of starting material I in 10 ml of dimethylformamide 1.67 g (8.58 mmol) of ethyl-α-bromoisobutyrate were added. The mixture was stirred at 80°C for 1 h and at 100-110°C for 23 h. The solution was diluted with water and the separated oily substance was extracted into dichloromethane. After washing and drying the

solvent was evaporated and the residue was purified by column chromatography, using a mixture of hexane-ethyl acetate (1:1) as eluent. Evaporation of the fractions containing the main product gave 0.80 g of the title compound as a gum.

Example 161

(R)-8-Methyl-5-(4-nitrophenyl)-7-(1,2,3-thiadiazol-5-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00279] To an ethereal solution containing diazomethane in high excess, a solution of 2.42 g (3.0 mmol) of starting material XII in 40 ml of tetrahydrofurane was added dropwise at -15°C. The solution was kept at room temperature for 5 days, when TLC showed full conversion. Evaporation gave a residue which was purified by column chromatography, using a mixture of hexane-ethyl acetate (3:1) as eluent. 2.13 g of the title product was resulted. Mp.: 175-176°C. $[\alpha]_D$: -96° (c=0.5; $CHCl_3$).

Example 162

(R)-5-(2-Bromo-3-methyl-4-nitrophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(R)-5-(2-Bromo-3-methyl-4-nitrophenyl)-7-(tert-butoxycarbonyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00280] The compound was prepared using 2-bromo-3-methylbenzaldehyde and tert-butylcarbazate according to a method published in the literature (Anderson *et al.*, *J. Am. Chem. Soc.* 117: 12358 (1995)).

[00281] MS:EI(70eV):$[M]^{+\cdot}$: 517/519, *m/z:* 417/419, 376/378, 57

[00282] CI:$[M+H]^+$: 518/520

Step B

(R)-5-(2-Bromo-3-methyl-4-nitrophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00283] Compound obtained in Step A was hydrolyzed according to method disclosed in Example 153, Step B.

[00284] MS:EI(70eV):$[M]^{+\cdot}$: 417/419, *m/z:* 402/404, 374/376, 338, 160

[00285] CI:[M+H]$^+$: 418/420, [M]$^{+\cdot}$: 417/419

Step C

(R)-5-(2-Bromo-3-methyl-4-nitrophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl chloride

[00286] The compound obtained in Step B was transformed into the title compound according to a method described for starting material XI.

[00287] MS:EI(70eV):[M]$^{+\cdot}$: 495/497, *m/z:* 460/462, 401/403, 355/357

[00288] CI:[M+H]$^+$: 496/498/500, *m/z:* 460/462

Step D

[00289] The title compound obtained in Step C was further reacted with acetic hydrazide according to a method described in Method B of Example 28 to give the title compound as a foam.

[00290] MS:EI(70eV):[M]$^{+\cdot}$: 515/517, *m/z:* 500/502, 401/403, 59

[00291] CI:[M+H]$^+$: 516/518

[00292]

Table 12.
2,3-Benzodiazepines containing aminophenyl group
(The ^{1}H NMR spectra were recorded at 500 MHz unless stated otherwise)

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
163	(R)-5-(4-Amino-3-methylphenyl)-8-methyl-7-(4,5-dihydro-thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	125-128	53 -282.0° (c=0.5, $CHCl_3$)
Method* B	^{1}H NMR (DMSO-d_6) d 1.10 (3H, d, 6.0 Hz), 2.06 (3H, s), 2.53 (1H , dd, 14.0 Hz, 10.0 Hz), 2.86 (1H, dd, 14.0 Hz, 4.5 Hz), 3.0 - 3.2 (2H, m), 3.93 (1H, m), 4.05 (1H, m), 4.85 (1H, m), 5.35 (2H, s), 6.04 (1H, s), 6.07 (1H, s), 6.55 (1H, s), 6.61 (1H, d, 8.5 Hz), 6.98 (1H, s), 7.13 (1H, d, br, 8.5 Hz), 7.22 (1H, s, br)		
164	(R)-5-(4-Amino-3-methylphenyl)-8-methyl-7-(thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	124-127	86 -619.5° (c=0.5, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) d 1.16 (3H, d, 6.0 Hz), 2.09 (3H, s), 2.59 (1H , dd,14.0 Hz, 10.5 Hz), 2.95 (1H, dd, 14.0 Hz, 5.5 Hz), 5.01 (1H, m), 5.47 (2H, s, br), 6.03 (1H, d, 1.1 Hz), 6.08 (1H, d,1.1 Hz), 6.58 (1H, s), 6.64 (1H, d, 8.0 Hz), 6.83 (1H, d, 3.5 Hz), 7.05 (1H, s), 7.21 (1H, dd, 8.0 Hz, 2.0 Hz), 7.28 (1H, d, 3.5 Hz), 7.31(1H, d, 2.0 Hz)		

* *See the general procedures given before Examples 60-118 for reduction of the nitro groups of various 2,3-benzodiazepines.*

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
165	(R)-5-(4-Amino-3-methylphenyl)-7-(5-ethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	129-133 (EtOH)	90 -534.9° (c=0.5, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) d 1.20 (3H, d, 6.1 Hz), 1.23 (3H, t, 7.6 Hz), 2.07 (3H, s), 2.58 (1H, dd, 14.0 Hz, 10.6 Hz), 2.85 (2H, q, 7.6 Hz), 2.95 (1H, dd, 14.0 Hz, 5.4 Hz), 4.93 (1H, m), 5.50 (2H, s, br), 6.03 (1H, d, 1.0 Hz), 6.08 (1H, d, 1.0 Hz), 6.57 (1H, s), 6.63 (1H, d, 8.4 Hz), 7.06 (1H, s), 7.20 (1H, dd, 8.4 Hz, 2.1 Hz), 7.25 (1H, d, 2.1 Hz) MS: EI(70eV): $[M]^{+\cdot}$: 421, *m/z*: 406, 293, 266 CI: $[M+H]^+$: 422, $[M]^{+\cdot}$: 421		
166	(R)-5-(4-Amino-3-methylphenyl)-8-methyl-7-(5-propyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	150-154 (EtOH)	56 -516.0° (c=0.5, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) d 0.91 (t, 7.5 Hz), 1.20 (3H, d, 6.1 Hz), 1.66 (2H, m), 2.08 (3H, s), 2.58 (1H, dd, 13.8 Hz, 10.6 Hz), 2.80 (2H, t, 7.2 Hz), 2.96 (1H, dd, 13.8 Hz, 5.1 Hz), 4.94 (1H, m), 5.50 (2H, s), 6.03 (1H, s), 6.08 (1H, s), 6.57 (1H, s), 6.64 (1H, d, 8.3 Hz), 7.05 (1H, s), 7.19 (1H, dd, 8.3 Hz, 2.1 Hz), 7.25 (1H, d, 2.1 Hz)		
167	(R)-5-(4-Amino-3-methylphenyl)-8-methyl-7-(1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	143-148 (EtOAc)	63 -527.3° (c=0.5, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) d 1.21 (3H, d, 6.1 Hz), 2.08 (3H, s), 2.61 (1H, dd, 13.6 Hz, 10.6 Hz), 3.00 (1H, dd, 13.6 Hz, 5.0 Hz), 5.00 (1H, m), 5.52 (2H, s, br), 6.03 (1H, d, 0.7 Hz), 6.08 (1H, d, 0.7 Hz), 6.58 (1H, s), 6.64 (1H, d, 8.3 Hz), 7.07 (1H, s), 7.20 (1H, dd, 8.3 Hz, 2.1 Hz), 7.28 (1H, d, 2.1 Hz), 8.78 (1H, s) MS: EI(70eV): $[M]^{+\cdot}$: 393, *m/z*: 378, 266 CI: $[M+H]^+$: 394, $[M]^{+\cdot}$: 393		
168	(R)-5-(4-Amino-3-methylphenyl)-8-methyl-7-(5-methoxymethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	171-172 (EtOH)	86 -540.0° (c=0.5, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) d 1.21 (3H, d, 6.1 Hz), 2.08 (3H, s), 2.60 (1H, dd, 14.0 Hz, 11.0 Hz), 2.97 (1H, dd, 14.0 Hz, 5.4 Hz), 4.57 (1H, d, 12.7 Hz), 4.60 (1H, d, 12.7 Hz), 4.98 (1H, m), 5.3 - 5.8 (2H), 6.03 (1H, s), 6.08 (1H, s), 6.58 (1H, s), 6.65 (1H, d, 8.6 Hz), 7.06 (1H, s), 7.21 (1H, dd, 8.6 Hz, 2.2 Hz), 7.26 (1H, d, 2.2 Hz)		
169	(R)-5-(4-Amino-3-methylphenyl)-7-(5-isopropyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	134-140	83 -518.8° (c=0.5, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) d 1.20 (3H, d, 6.2 Hz), 1.26 (3H, d, 6.9 Hz), 1.28 (3H, d, 6.9 Hz), 2.07 (3H, s), 2.58 (1H, dd, 13.8 Hz, 10.8 Hz), 2.95 (1H, dd, 13.8 Hz, 5.5 Hz), 3.18 (1H, m), 4.94 (1H, m), 5.51 (2H, s, br), 6.03 (1H, s), 6.08 (1H, s), 6.57 (1H, s), 6.64 (1H, d, 8.4 Hz), 7.06 (1H, s), 7.21 (1H, dd, 8.4 Hz, 2.1 Hz), 7.24 (1H, d, 2.1 Hz)		
170	(R)-5-(4-Amino-3-methylphenyl)-7-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	124-128	47 -504.1° (c=0.5, $CHCl_3$)

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
Method B	^{1}H NMR (DMSO-d_6) d 0.86 (2H, m), 1.03 (2H, m), 1.16 (3H, d, 6.2 Hz), 2.07 (3H, s), 2.23 (1H, m), 2.57 (1H , dd, 14.0 Hz, 10.8 Hz), 2.95 (1H, dd, 14.0 Hz, 5.5 Hz), 4.92 (1H, m), 5.50 (2H, s), 6.03 (1H, s), 6.08 (1H, s), 6.55 (1H, s), 6.64 (1H, d, 8.3 Hz), 7.05 (1H, s), 7.19 (1H, dd, 8.3 Hz, 2.1 Hz), 7.23 (1H, d, 2.1 Hz)		
171	(R)-5-(4-Amino-3-methylphenyl)-7-(5-hydroxymethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	184-186	75 -540.0° (c=0.5, $CHCl_3$)
Method A	^{1}H NMR (DMSO-d_6) d 1.20 (3H, d, 6.1 Hz), 2.08 (3H, s), 2.60 (1H , dd, 13.9 Hz, 10.6 Hz), 2.97 (1H, dd, 13.9 Hz, 5.3 Hz), 4.61 (2H, d, 5.8 Hz), 4.95 (1H, m), 5.52 (2H, s), 5.81 (1H, t, 5.8 Hz), 6.03 (1H, s), 6.08 (1H, s), 6.58 (1H, s), 6.65 (1H, d, 8.5 Hz), 7.06 (1H, s), 7.19 (1H, dd, 8.5 Hz, 2.0 Hz), 7.26 (1H, d, 2.0 Hz)		
172	(R)-7-(5-Acetoxymethyl-1,3,4-thiadiazol-2-yl)-5-(4-amino-3-methylphenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	204-206 (EtOH)	45 -560.0° (c=0.5, $CHCl_3$)
Method E	^{1}H NMR (DMSO-d_6) d 1.21 (3H, d, 6.2 Hz), 2.07 (3H, s), 2.08 (3H, s), 2.60 (1H , dd, 14.0 Hz, 11.0 Hz), 2.97 (1H, dd, 14.0 Hz, 5.4 Hz), 4.99 (1H, m), 5.20 (1H, d, 13.1 Hz), 5.24 (1H, d, 13.1 Hz), 5.55 (2H, s), 6.03 (1H, s), 6.09 (1H, s), 6.59 (1H, s), 6.65 (1H, d, 8.4 Hz), 7.06 (1H, s), 7.21 (1H, dd, 8.4 Hz, 2.1 Hz), 7.26 (1H, d, 2.1 Hz)		
173	(R)-5-(4-Amino-3-methylphenyl)-7-(5-cyanomethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	135-140	25 -517.9° (c=0.5, $CHCl_3$)
Method A	^{1}H NMR (DMSO-d_6) d 1.21 (3H, d, 6.2 Hz), 2.08 (3H, s), 2.61 (1H , dd, 13.9 Hz, 11.0 Hz), 2.99 (1H, dd, 13.9 Hz, 5.5 Hz), 4.40 (2H, s), 4.96 (1H, m), 5.55 (2H, s), 6.03 (1H, d, 0.7 Hz), 6.09 (1H, d, 0.7 Hz), 6.59 (1H, s), 6.65 (1H, d, 8.3 Hz), 7.06 (1H, s), 7.21 (1H, dd, 8.3 Hz, 1.8 Hz), 7.26 (1H, d, 1.8 Hz)		
174	(R)-5-(4-Amino-3-methylphenyl)-8-methyl-7-(5-methylthiomethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	177-180 (EtOH)	57 -496.0° (c=0.5, $CHCl_3$)
Method A	^{1}H NMR (DMSO-d_6) d 1.21 (3H, d, 6.1 Hz), 2.03 (3H, s), 2.08 (3H, s), 2.60 (1H , dd, 13.8 Hz, 10.6 Hz), 2.97 (1H, dd, 13.8 Hz, 5.3 Hz), 3.91 (1H, d, 14.7 Hz), 3.95 (1H, d, 14.7 Hz), 4.96 (1H, m), 5.52 (2H, s), 6.03 (1H, d, 0.9 Hz), 6.09 (1H, d, 0.9 Hz), 6.59 (1H, s), 6.65 (1H, d, 8.4 Hz), 7.06 (1H, s), 7.21 (1H, dd, 8.4 Hz, 2.0 Hz), 7.25 (1H, d, 2.0 Hz)		
175	(R)-5-(4-Amino-3-methylphenyl)-7-(5-ethoxycarbonyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	135-140	86 -606.3° (c=0.5, $CHCl_3$)
Method E	^{1}H NMR (DMSO-d_6) d 1.15 (3H, d, 6.2 Hz), 1.30 (3H, t, 7.1 Hz), 2.09 (3H, s), 2.64 (1H , dd, 13.8 Hz, 11.3 Hz), 2.99 (1H, dd, 13.8 Hz, 5.4 Hz), 4.30 (2H, m), 5.11 (1H, m), 5.65 (2H, s), 6.04 (1H, s), 6.09 (1H, s), 6.61 (1H, s), 6.65 (1H, d, 8.3 Hz), 7.08 (1H, s), 7.25 (1H, dd, 8.3 Hz, 2.0 Hz), 7.26 (1H, d, 2.0 Hz)		
176	(R)-5-(4-Amino-3-methylphenyl)-7-(5-aminomethyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	139-140 (EtOH)	31 -482.2° (c=0.5, $CHCl_3$)

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
Method B	^{1}H NMR (DMSO-d_6) d 1.21 (3H, d, 6.0 Hz), 2.08 (3H, s), 2.59 (1H , dd, 13.9 Hz, 13.9 Hz), 2.95 (1H, dd, 13.9 Hz, 5.1 Hz), 3.87 (2H, s), 4.95 (1H, m), 5.50 (2H, s), 6.03 (1H, s), 6.07 (1H, s), 6.57 (1H, s), 6.65 (1H, d, 8.1 Hz), 7.05 (1H, s), 7.21 (1H, d, br, 8.1 Hz), 7.26 (1H, s, br)		
177	(R)-5-(4-Amino-3-methylphenyl)-8-methyl-7-{5-[1-(1E)-propen-1-yl]-1,3,4-thiadiazol-2-yl}-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	139-143	65 -498.9° (c=0.5, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) d 1.21 (3H, d, 6.2 Hz), 1.86 (1H, dd, 6.8 Hz, 1.8 Hz), 2.08 (3H, s), 2.59 (1H , dd, 14.0 Hz, 10.8 Hz), 2.98 (1H, dd, 14.0 Hz, 5.4 Hz), 4.98 (1H, m), 5.53 (2H, s, br), 6.03 (1H, s), 6.08 (1H, s), 6.32 (1H, dq, 15.7 Hz, 6.8 Hz), 6.55 (1H, dq, 15.7 Hz, 1.8 Hz), 6.57 (1H, s), 6.44 (1H, d, 8.4 Hz), 7.06 (1H, s), 7.22 (1H, dd, 8.4 Hz, 2.1 Hz), 7.26 (1H, d, 2.1 Hz)		
178	(R)-5-(4-Amino-3-methylphenyl)-7-(5-hexyl-1,3,4-thiadiazol-2-yl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	180-181	75 -485.2° (c=0.5, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) d 0.84 (3H, t, 7.0 Hz), 1.20 (3H, d, 6.1 Hz), 1.2-1.3 (6H, m), 1.62 (2H, m), 2.07 (3H, s), 2.58 (1H , dd, 13.9 Hz, 10.5 Hz), 2.82 (2H, t, 7.5 Hz), 2.95 (1H, dd, 13.9 Hz, 5.4 Hz), 4.94 (1H, m), 5.49 (2H, s), 6.03 (1H, s), 6.08 (1H, s), 6.57 (1H, s), 6.64 (1H, d, 8.4 Hz), 7.05 (1H, s), 7.19 (1H, dd, 8.4 Hz, 2.2 Hz), 7.25 (1H, d, 2.2 Hz)		
179	(R)-5-(4-Amino-3-methylphenyl)-8-methyl-(5,6-dihydro-5-oxo-4H-1,3,4-thiadiazin-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	175-180	61 -686.0° (c=0.5, $CHCl_3$)
Method B	^{1}H NMR (DMSO-d_6) d 1.15 (3H, d, 6.4 Hz), 2.05 (3H, s), 2.48 (1H, dd, 13.8 Hz, 10.4 Hz), 2.85 (1H, dd, 13.8 Hz, 5.3 Hz), 3.32 (2H, s), 4.75 (1H, m), 5.42 (2H, s), 6.04 (1H, s), 6.07 (1H, s), 6.55 (1H, s), 6.61 (1H, d, 8.4 Hz), 6.99 (1H, s), 7.15 (1H, dd, 8.4 Hz, 1.8 Hz), 7.26 (1H, d, 1.8 Hz), 10.47 (1H, s)		
180	(R)-5-(4-Aminophenyl)-8-methyl-7-(1,3,4-oxadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	187-190	78 -604.0° (c=0.5, $CHCl_3$)
Method A	^{1}H NMR ($CDCl_3$) d 1.45 (3H, d, 6.0 Hz), 2.73 (1H , dd, 14.0 Hz, 10.5 Hz), 2.86 (1H, dd, 14.0 Hz, 5.5 Hz), 3.99 (2H, s, br), 4.94 (1H, m), 5.98 (1H, d, 1.0 Hz), 6.02 (1H, d, 1.0 Hz), 6.64 (1H, s), 6.68 (2H, d, 8.0 Hz), 6.82 (1H, s), 7.56 (2H, d, 8.0 Hz), 7.99 (1H, s)		
181	(R)-5-(4-Amino-3-methylphenyl)-8-methyl-7-(5-methyl-1,3,4-oxadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	140-145	85 -554.8° (c=0.5, $CHCl_3$)
Method B	MS: EI(70eV): $[M]^{+\cdot}$: 391, *m/z*: 266 CI: $[M+H]^+$: 392		
182	(R)-5-(4-Amino-3-chlorophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	98-100	92 -266.0° (c=0.5, $CHCl_3$)
Method C	^{1}H NMR (DMSO-d_6) d 1.18 (3H, d, 6.0 Hz), 2.50 (3H, s), 2.65 (1H , dd, 14.0 Hz, 9.9 Hz), 2.98 (1H, dd, 14.0 Hz, 4.9 Hz), 4.95 (1H, m), 5.95 (2H, s), 6.05 (1H, s), 6.09 (1H, s), 6.63 (1H, s), 6.83 (1H, d, 8.6 Hz), 7.07 (1H, s), 7.24 (1H, dd, 8.6 Hz, 2.0 Hz), 7.44 (1H, d, 2.0 Hz) MS: EI(70eV): $[M]^{+\cdot}$: 427/429, *m/z*: 412/414, 313/315, 286/288, 160 CI: $[M+H]^+$: 428/30, $[M]^{+\cdot}$: 427/429		

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
183	(R)-5-(4-Amino-3-chlorophenyl)-8-methyl-7-(5-methoxymethyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	105-109	91 -350.0° (c=0.5, $CHCl_3$)
Method C	^{1}H NMR (DMSO-d_6) d 1.20 (3H, d, 6.1 Hz), 2.67 (1H , dd, 14.1 Hz, 10.3 Hz), 3.00 (1H, dd, 14.1 Hz, 5.4 Hz), 3.32 (3H, s), 4.58 (1H, d, 13.0 Hz), 4.62 (1H, d, 13.0 Hz), 5.01 (1H, m), 5.98 (2H, s, br), 6.05 (1H, s), 6.09 (1H, s), 6.64 (1H, s), 6.84 (1H, d, 8.4 Hz), 7.07 (1H, s), 7.29 (1H, dd, 8.4 Hz, 1.8 Hz), 7.44 (1H, d, 1.8 Hz) MS: EI(70eV): $[M]^{+\cdot}$: 457/459, *m/z*: 442/444, 313/315, 286/288, 160 CI: $[M+H]^+$: 458/60, $[M]^{+\cdot}$: 457/459		
184	(R)-5-(4-Amino-2-bromo-3-methylphenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	foam	98
Method A	^{1}H NMR ($CDCl_3$) d 1.25 (3H, d, 6.2 Hz), 2.25 (3H, s), 2.53 (3H, s), 2.93 (1H , dd, 14.6 Hz, 7.3 Hz), 3.25 (1H, dd, 14.6 Hz, 3.1 Hz), 3.4 - 4.3 (2H), 5.43 (1H, m), 5.92 (1H, d, 1.4 Hz), 5.93 (1H, d, 1.4 Hz), 6.36 (1H, s), 6.69 (1H, d, 8.1 Hz), 6.72 (1H, s), 7.12 (1H, d, 8.1 Hz) MS: EI(70eV): $[M]^{+\cdot}$: 485/487, *m/z*: 470/472, 406, 265, 219 CI: $[M+H]^+$: 486/488		
185	(±)-5-(4-Aminophenyl)-8-methyl-7-(3-methyl-isoxazol-5-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	100-103	87
Method C	^{1}H NMR (DMSO-d_6) d 1.16 (3H, d, 6.5 Hz), 2.07 (3H, s), 2.45 (1H , dd, 14.0 Hz, 11.5 Hz), 2.88 (1H, dd, 14.0 Hz, 6.0 Hz), 4.58 (1H, m), 5.26 (1H, s), 5.70 (2H, s), 6.02 (1H, s), 6.07 (1H, s), 6.56 (1H, s), 6.58 (2H, d, 8.5 Hz), 7.03 (1H, s), 7.36 (2H, d, 8.5 Hz) MS: EI(70eV): $[M]^{+\cdot}$: 376, *m/z*: 306, 265, 252, 82, 54 CI: $[M+H]^+$: 377, $[M]^{+\cdot}$: 376		
186	(R)-5-(4-Aminophenyl)-8-methyl-7-(1,2,3-thiadiazol-5-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	220-221	33 -705.0° (c=0.5, $CHCl_3$)
Method A	^{1}H NMR (DMSO-d_6) d 1.18 (3H, d, 6.1 Hz), 2.60 (1H , dd, 13.8 Hz, 11.4 Hz), 2.95 (1H, dd, 13.8 Hz, 5.1 Hz), 4.75 (1H, m), 5.81 (2H, s, br), 6.03 (1H, s), 6.08 (1H, s), 6.59 (1H, s), 6.61 (2H, d, 8.4 Hz), 7.08 (1H, s), 7.35 (2H, d, 8.4 Hz), 8.10 (1H, s) MS: EI(70eV): $[M]^{+\cdot}$: 379, *m/z:* 351, 336, 279, 252 CI: $[M+H]^+$: 380, *m/z:* 352		
187	(±)-5-(4-Aminophenyl)-8-methyl-7-(2-methyl-1,3-oxazol-5-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	148-150	88
Method A	^{1}H NMR (DMSO-d_6) d 1.07 (3H, d, 5.3 Hz), 2.23 (3H, br), 2.40 (1H , dd, 13.7 Hz, 7.7 Hz), 2.83 (1H, dd, 13.7 Hz, 5.6 Hz), 4.31 (1H, m), 5.58 (s, br), 6.03 (1H, s), 6.05 (1H, s), 6.54 (2H, d, 8.2 Hz), 6.57 (1H, s), 7.00 (1H, s), 7.28 (2H, d, 8.2 Hz) MS: EI(70eV): $[M]^{+\cdot}$: 376, *m/z*: 335, 306, 265, 252 CI: $[M+H]^+$: 377		
188	(±)-5-(4-Aminophenyl)-8-methyl-7-(2,4-dimethyl-1,3-oxazol-5-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	180-182	92

Number of Example	Name	Mp. (°C) Solvent of recrystall.	Yield (%) $[\alpha]_D$
Method A	^{1}H NMR (DMSO-d_6) d 0.94 (3H, d, 6.1 Hz), 1.76 (3H, s), 2.29 (3H, s), 2.43 (1H , dd, 13.8 Hz, 3.3 Hz), 2.79 (1H, dd, 13.8 Hz, 6.6 Hz), 4.13 (1H, m), 5.53 (s, br), 6.07 (1H, s), 6.08 (1H, s), 6.52 (2H, d, 8.4 Hz), 6.58 (1H, s), 6.99 (1H, s), 7.18 (2H, d, 8.4 Hz) MS: EI(70eV): $[M]^{+\cdot}$: 390, *m/z*: 349, 334, 306, 279, 265, 252 CI: $[M+H]^+$: 391, $[M]^{+\cdot}$: 390		
189	(R)-5-(4-Amino-3,5-dimethylphenyl)-8-methyl-7-(thiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	202-203	75 -686.0° (c=0.3, $CHCl_3$)
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 406, *m/z*: 391, 307, 280		
190	(R)-5-(4-Amino-3,5-dimethylphenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	280-281	74 -538.0° (c=0.5, $CHCl_3$)
Method A	^{1}H NMR (DMSO-d_6) d 1.18 (3H, d, 6.1 Hz), 2.11 (6H, s), 2.49 (3H, s), 2.57 (1H , dd, 13.9 Hz, 10.8 Hz), 2.95 (1H, dd, 13.9 Hz, 5.1 Hz), 4.93 (1H, m), 5.19 (2H, s, br), 6.03 (1H, d, 0.5 Hz), 6.08 (1H, d, 0.5 Hz), 6.56 (1H, s), 7.05 (1H, s), 7.12 (2H, s) MS: EI(70eV): $[M]^{+\cdot}$: 421, *m/z*: 406, 307, 306, 280 CI: $[M+H]^+$: 422		
191	(R)-5-(4-Amino-3,5-dimethylphenyl)-8-methyl-7-(5-methyl-1,3,4-oxadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine	148-150	87 -705.0° (c=0.5, $CHCl_3$)
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 405, *m/z*: 280, 245, 134, 83, 77 CI: $[M+H]^+$: 406		
192	(R)-5-(4-Aminophenyl)-8-methyl-7-(2-methyl-3-oxo-2,3-dihydro-1,2,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	185-190	60 -45.0° (c=0.47, $CHCl_3$)
Method A	^{1}H NMR (DMSO-d_6) d 1.19 (3H, d, 6.5 Hz), 2.69 (1H , dd, 14.0 Hz, 10.0 Hz), 3.00 (1H, dd, 14.0 Hz, 4.5 Hz), 3.05 (3H, s), 4.89 (1H, m), 5.81 (2H, s, br), 6.05 (1H, s), 6.08 (1H, s), 6.58 (2H, d, 8.5 Hz), 6.59 (1H, s), 7.06 (1H, s), 7.26 (2H, d, 8.5 Hz) MS: EI(70eV): $[M]^{+\cdot}$: 409, *m/z*: 279, 252 CI: $[M+H]^+$: 410, $[M]^{+\cdot}$: 409		
193	(±)-5-(4-Aminophenyl)-8-methyl-7-(5,5-dimethyl-4-oxo-4,5-dihydrothiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo-[4,5-h][2,3]benzodiazepine	124-130 amorphous	75
Method A	MS: EI(70eV): $[M]^{+\cdot}$: 422, *m/z*: 407, 279, 252 CI: $[M+H]^+$: 423		

Example 194

(R)-7-(4,5-Dihydro-thiazol-2-yl)-5-(4-chlorophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(R)-7-(tert-Butoxycarbonyl)-5-(4-chlorophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00293] The compound was prepared according to a synthesis described in literature (Anderson *et al., J. Am. Chem. Soc.* 117: 12358 (1995)) with the exception that tert-butylcarbazate and 4-chlorobenzaldehide were used instead of acetic hydrazide and 4-nitrobenzaldehide, respectively. The title product was isolated as a foam and used for the next step.

Step B

(R)-5-(4-Chlorophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00294] 11.0 g (28.2 mmol) of the product obtained in Step A was dissolved in 120 ml of ethyl acetate containing 10% hydrochloric acid and stirred for 3 h, then the solution was washed with sodium carbonate and water. After drying and evaporation the crude product was recrystallized from ethyl acetate to yield 5.07 g (57%) of the title compound. Mp.: 185-187°C; $[\alpha]_D$: +241.0° (c=0.5; $CHCl_3$).

Step C

(R)-5-(4-Chlorophenyl)-8-methyl-7-thiocarbamoyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00295] A mixture containing 1.57 g (5.0 mmol) of the product obtained in Step B, 0.73 g (7.5 mmol) of potassium thiocyanate and 16 ml of acetic acid was stirred at 110°C for 3 h. After cooling water was added and the precipitated crystals were filtered off, washed with water and dried to yield 1.73 g (92%) of the title compound. Mp.: 208-212°C.

Step D

[00296] The compound obtained in Step C (1.0 g, 2.66 mM) was reacted with 2.20 g (10.7 mmol) of 2-bromoethylamine hydrobromide in 5 ml of dimethylformamide according to the method described in Example 9. The product was isolated by column chromatography and an additional recrystallization from ethyl acetate to yield 0.26 g (25%) of the title compound. Mp.: 216-219°C; $[\alpha]_D$: +326.7°(c=0.5; $CHCl_3$).

[00297] ^{1}H NMR (DMSO-d_6) δ 1.11 (3H, d, 5.7 Hz), 2.79 (1H , dd, 14.7 Hz, 6.4 Hz), 3.16 (1H, dd, 14.7 Hz, 1.7 Hz), 3.25 (2H, m), 4.16 (2H, m), 4.28 (2H, m), 5.25 (1H, m), 5.99 (2H, s), 6.59 (1H, s), 6.71 (1H, s) 7.34 (2H, d, 8.0 Hz), 7.53 (2H, d, 8.0 Hz)

Example 195

(R)-5-(4-Chlorophenyl)-8-methyl-7-(2-thiazolyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00298] The compound obtained in Step C of Example 194 (0.55 g, 1.47 mmol) was reacted with 0.22 ml (1.47 mmol) of bromoacetaldehyde diethyl acetal according to the method described in Example 1. The crude product was purified by column chromatography using a mixture of n-hexane-ethyl acetate (2:1) as eluent. After concentration of the fractions containing the title compound the residue was treated with water to yield 0.40 g (68%) of the title compound. Mp.: 116-117°C; $[\alpha]_D$: +118.6° (c=0.5; $CHCl_3$).

[00299] ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, d, 6.4 Hz), 2.83 (1H , dd, 14.6 Hz, 7.2 Hz), 3.18 (1H, dd, 14.6 Hz, 3.4 Hz), 5.38 (1H, m), 6.01 (2H, s), 6.61 (1H, s), 6.69 (1H, d, 3.7 Hz), 6.78 (1H, s), 7.32 (1H, d, 3.7 Hz), 7.38 (2H, d, 8.6 Hz), 7.58 (2H, d, 8.6 Hz)

Example 196

(R)-5-(4-Chlorophenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

Step A

(R)-5-(4-Chlorophenyl)-8-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine-7-carbothioyl chloride

[00300] The compound obtained in Step B of Example 194 (2.20 g, 7.0 mmol) was reacted according to the method described for starting compound XI. The crude product was purified by column chromatography using a mixture of n-hexane-ethyl acetate (4:1) as eluent to yield 1.38 g (49%) of the title compound as a solid foam.

Step B

[00301] 1.0 g (2.48 mmol) of the product obtained in Step A was used to prepare the title compound according to a method described in Example 28, Method B. The product, isolated by column chromatography, was solidified by water to give 0.42 g (52%), Mp.: 105-108°C; $[\alpha]_D$: +103.2° (c=0.5; $CHCl_3$).

[00302] ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, d, 6.2 Hz), 2.61 (3H, s), 2.84 (1H, dd, 14.3 Hz, 7.1 Hz), 3.18 (1H, dd, 14.3 Hz, 3.6 Hz), 5.35 (1H, m), 6.02 (2H, s), 6.57 (1H, s), 6.79 (1H, s), 7.38 (2H, d, 8.2 Hz), 7.52 (2H, d, 8.2 Hz)

Example 197

(R)-5-(4-Acetylamino-3-methylphenyl)-8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine

[00303] The compound of Example 119 was acetylated according to the general method described for Examples 120-131. Mp.: 267-269 °C. Yield: 67%; $[\alpha]_D$: -121.0° (c=0.5; $CHCl_3$).

[00304] ^{1}H NMR (DMSO-d_6) δ 1.16 (3H, d, 6.1 Hz), 2.10 (3H, s), 2.25 (3H, s), 2.50 (3H, s), 2.79 (1H, dd, 14.0 Hz, 8.2 Hz), 3.09 (1H, dd, 14.0 Hz, 4.0 Hz), 5.08 (1H, m), 6.07 (1H, s), 6.09 (1H, s), 6.55 (1H, s), 7.07 (1H, s), 7.31 (1H, d, 8.3 Hz), 7.38 (1H, s, br), 7.59 (1H, d, br, 8.3 Hz), 9.36 (1H, s)

Example 198

(R)-1-Methyl-3{2-methyl-4-[8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepin-5-yl]}-phenylurea

[00305] The substance (1.03 g, 2.53 mmol) obtained in Example 119 was reacted with 0.75 ml (12.6 mmol) of methyl isocyanate in 20 ml of dichloromethane for 6 days at RT. Evaporation of the solvent gave a crude product which was purified by column chromatography, using a mixture of hexane-ethyl acetate (2:1) as eluent to give 0.67 g (57%) of the title compound. Mp.: 237-242 °C; $[\alpha]_D$: -140.0° (c=0.5; $CHCl_3$).

[00306] ^{1}H NMR (DMSO-d_6) δ 1.17 (3H, d, 6.4 Hz), 2.21 (3H, s), 2.51 (3H, s), 2.66 (3H, d, 4.6 Hz), 2.71 (1H, dd, 14.2 Hz, 9.4 Hz), 3.04 (1H, dd, 14.2 Hz, 4.5 Hz), 5.02 (1H, m), 6.05 (1H, d, 0.9 Hz), 6.08 (1H, d, 0.9 Hz), 6.55 (1H, s), 6.56 (1H, q, 4.6 Hz), 7.07 (1H, s), 7.30 (1H, dd, 8.4 Hz, 2.0 Hz), 7.34 (1H, d, 2.0 Hz), 7.82 (1H, s), 8.00 (1H, d, 8.4 Hz)

Example 199

(R)-2-Methyl-4-[8-methyl-7-(5-methyl-1,3,4-thiadiazol-2-yl)-8,9-dihydro-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepin-5-yl]-phenylcarbamic acid ethyl ester

[00307] The substance (0.90 g, 2.21 mmol) obtained in Example 119 was reacted with ethyl chloroformate (0.30 ml, 3.15 mmol) in dichloromethane in the presence of 0.40 ml (2.88 mmol) of triethylamine for 6 h at RT. The solution was washed with diluted hydrochloric acid and sodium hydrogen carbonate solution, dried and evaporated to dryness. The residue was

purified by column chromatography using a mixture of hexane-ethyl acetate (2:1) as eluent to give 0.45 g (42%) of the title product. Mp.: 241-244 °C; $[\alpha]_D$: -180.0°(c=0.5; $CHCl_3$).

[00308] ^1H NMR (DMSO-d_6) δ 1.15 (3H, d, 6.1 Hz), 1.25 (3H, t, 7.0 Hz), 2.25 (3H, s), 2.51 (3H, s), 2.78 (1H , dd, 14.3 Hz, 8.7 Hz), 3.05 (1H, dd, 14.3 Hz, 4.3 Hz), 4.13 (2H, q, 7.0 Hz), 5.07 (1H, m), 6.06 (1H, d, 0.7 Hz), 6.08 (1H, d, 0.7 Hz), 6.55 (1H, s), 7.07 (1H, s), 7.31 (1H, dd, 8.3 Hz, 2.0 Hz), 7.36 (1H, d, 2.0 Hz), 7.53 (1H, d, 8.3 Hz), 8.96 (1H, s)

[00309] Further results with compounds of the present invention are collected in the following tables, exemplifying the AMPA antagonistic activity of compounds of formula(I). (The corresponding *in vitro* and *in vivo* investigational methods and related references were described and cited earlier in this application.)

Table 13. (Supplement to Table 1)
Inhibition of the "spreading depression" in chicken retina

Compound (Number of example) / IC_{50} μM					
119	**165**	**166**	**167**	**168**	**182**
0.069	0.113	0.201	0.064	0.082	0.020

Table 14. (Supplement to Table 2)
Inhibition of ion-currents caused by 5 μM AMPA determined by the whole cell patch clamp method

Compound (Number of example) / IC_{50} μM					
119	**165**	**166**	**167**	**168**	**182**
0.026	0.024	0.028	0.070	0.011	0.031

Table 15. (Supplement to Table 3)
Investigation of the anticonvulsive activity in mice

Method	Compound (Number of example) / ED_{50} mg/kg po.					
	119	**165**	**166**	**167**	**168**	**182**
MES 60'	2.87	3.99	4.01	5.85	4.49	6.17
MES 30'	2.15	2.39	4.54	4.78	2.21	5.08
Pentetrazol	5.00	10.10	9.18	9.66	6.90	8.37

Strychnine	8.40	10.20	7.29	10.50	10.00	5.90
Bemegride	5.70	10.00	7.77	8.33	6.70	7.94
Bicuculline	2.50	5.79	13.30	12.70	10.60	8.44
Nicotine	6.30	18.60	21.80	10.80	17.70	24.20
4-AP	2.68	8.60	6.81	10.80	4.60	5.44
3-MPA	3.37	8.53	9.92	10.30	4.62	7.57

Abbreviations: MES = maximal electroshock seizure; 4-AP = 4-aminopyridine; 3-MPA = 3-mercapto-propionic acid

Table 16. (Supplement to Table 4)
Muscle relaxant activity in mice

Compound (Number of example)	Inclined screen ED_{50} ip. (mg/kg)	Rotarod ED_{50} ip. (mg/kg)
119	2.49	0.51
165	2.94	0.91
166	3.27	0.86
167	4.24	0.80
168	3.58	0.80
182	5.84	2.61

Table 17. (Supplement to Table 5)
Inhibition of focal ischemia in rats

Compound (Number of example)	Dose mg/kg iv. (6x in every 30 min)	Decrease of the infracted area in % compared to that of the control			
		30 min	120 min	180 min	240 min
		Time of first treatment after occlusion			
119	0.5		7		
	1.0		38		
	1.5		51*	21	
	2.0		56*	44**	21

* $p<0.05$; ** $p<0.01$; calculated with Dunnett test following ANOVA (Dunnett *J. Amer. Statist. Ass.* 50:1096 (1955))

[00310] Compounds of the invention were further investigated in the autoimmune encephalomyelitis model in rats as outlined in this description before, with the variance that 10 animals were used in each group, of weights 140-160 g (Lewis rats, female). The results are shown in Tables 19 and 20.

Table 18. (Supplement to Table 6)

Effect of 2,3-benzodiazepines possessing AMPA antagonist activity on the clinical symptoms of autoimmune encephalomyelitis in Lewis rats

Compound (Number of example)	Dose		Neurological symptoms (change compared to controls, %) Female rats	
	mg/kg i.p.	mg/kg p.o.	0-8 day	0-14 day
119	3.75		-97***	-90**
	1.875		-72*	-71**
	1.0		-75**	-72**
	0.5		-33	-35
	0.2		-36	-37
		3.75	-64***	-61***
		1.875	-50**	-50**
		1.0	-20	-23
		0.5	+2	-1
166		7.5	-51*	-53*
		3.75	-6	-9
168		7.5	-55*	-56*
		3.75	-16	-23

For statistics see Table 20.

Table 19. (Supplement to Table 7)

Effect of 2,3-benzodiazepine derivatives possessing AMPA antagonistic character on the histological and clinical symptoms of autoimmune encephalomyelitis in Lewis rats on day 24 after immunization.

Compound (Number of example)	Dose		Histopathological symptoms (change %)	Neurological symptoms (change %)
	mg/kg i.p.	mg/kg p.o.	Female rats	
119	3.75		+3	-90**
	1.875		-8	-71**
	1.0		-3	-72**
	0.5		-13	-35
	0.2		+2	-37
		3.75	-32	-61***
		1.875	-42	-50**
		1.0	-21	-23
		0.5	-16	-1

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Mann-Whitney test).

Table 20. (Supplement to Table 8)

Effect of 2,3-benzodiazepine derivatives possessing AMPA antagonistic character on the tremor of CD1 mice induced by different chemical agents.

Compound (Number of example)	ED_{50} (mg/kg po.)	
	Oxotremorin 1 mg/kg ip.	GYKI 20039 10 mg/kg ip.
119	1.38(0.80-2.38)	2.21(1.37-3.56)
165	4.63(3.66-5.85)	5.34(3.90-7.31)
166	2.74(1.97-3.00)	4.54(3.69-5.58)
167	4.81(3.45-6.72)	7.73(4.99-11.98)
168	3.29(2.63-4.12)	4.11(3.22-5.45)
182	2.66(1.24-5.72)	3.64(2.37-5.57)

Table 21. (Supplement to Table 9)

Effect of the compound described in Example 119 on the bronchial hypersensitivity and the eosinophilia of the airways of BN-rats sensitized with ovalbumin and antigen challenged by inhalation (mean±SE, N=10, p determined by Student's t-test).

			Compound (Number of example)
Parameter	Control	Challenge	**119** 3.0 mg/kg po
ED_{50}*	5.19±0.07	5.97±0.29	4.35±0.36
p	*0.001*		*0.001*
MAX**	100±0	154±21	82±7
p	*0.001*		*0.009*
Eosinophil***	0.15±0.03	1.17±0.18	1.16±0.24
p	*0.001*		*NS*[t]

* acetylcholine (Ach) concentration (-log M) which causes a 50% contraction compared to the control

** relative contraction compared to the control at a maximal Ach concentration

*** BALF eosinophil number ($x10^6$/ml)

[t] not significant ($p > 0.05$)

Equivalents

[00311] While the claimed invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one of ordinary skill in the art that various changes and modifications can be made to the claimed invention without departing from the spirit and scope thereof. Thus, for example, those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific substances and procedures described herein. Such equivalents are considered to be within the scope of this invention, and are covered by the following claims.